CONCLUSION ON PESTICIDES PEER REVIEW

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

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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 Greece and co-rapporteur Member State Cyprus for the pesticide active substance fenamiphos 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 fenamiphos as a nematicide in fruiting vegetables (i.e. tomato, aubergine, cucumber, pepper and courgette), herbaceous ornamentals and in nursery stock (both perennial and herbaceous species). 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: fenamiphos, peer review, risk assessment, pesticide, nematicide

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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. Fenamiphos 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), Greece, and co-rapporteur Member State (co-RMS), Cyprus, received an application from AMVAC Netherlands B.V. for the renewal of approval of the active substance fenamiphos. Complying with Article 8 of the Regulation, the RMS checked the completeness of the dossier and informed the applicant, the co-RMS (Cyprus), the European Commission and the European Food Safety Authority (EFSA) about the admissibility.

The RMS provided its initial evaluation of the dossier on fenamiphos in the renewal assessment report (RAR), which was received by EFSA on 2 October 2017. In accordance with Article 12 of the Regulation, EFSA distributed the RAR to the Member States and the applicant, AMVAC Netherlands B.V., for comments on 21 December 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 February 2018.

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

In accordance with Article 13(1) of the Regulation, EFSA should adopt a conclusion on whether fenamiphos 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 fenamiphos as a nematicide by drip irrigation in permanent greenhouses fruiting vegetables (i.e. tomato, aubergine, cucumber, pepper and courgette), herbaceous ornamentals and in nursery stock (both perennial and herbaceous species), in Southern Europe only, as proposed by the applicant. Full details of the representative uses can be found in Appendix A of this report.

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

A data gap for screening of biological activity of metabolites M13 and M14 was identified for all representative uses except for geoclimatic conditions of monitoring regions in Greece.

A data gap was identified for a search of the scientific peer-reviewed open literature on metabolites M12, M13 and M14 dealing with side effects on the environment and non-target species.

In the section identity, physical/chemical properties, analytical methods data gaps were identified for analytical methods for monitoring of the residue definition in dry, high acidic and high oil content commodities; for a confirmatory method of the method for monitoring of fenamiphos residues in surface water; for additional validation data for the submitted monitoring method in air or a new method with a LOQ in compliance with the requirements for the operators, workers, residents and bystanders risk assessment and for analytical methods for monitoring of M11, M13 and M12 in body fluids and tissues.

The toxicological profile of fenamiphos in mammalian species is typical of organophosphate substances with cholinergic effects as main toxicological endpoints. The following data gaps were identified: exclusion of genotoxic potential for mammalian metabolites M01 and M02, exclusion of genotoxicity for the rotational crop metabolite M09, toxicological characterisation for the groundwater metabolites M13 and M14, and *in vitro* interspecies hepatic metabolism leading to an issue not finalised.

In the residues section, several data gaps were identified in the following areas: storage stability, processing trials and field trials on rotational crops. Although the overall consumer risk assessment is provisional, an acute consumer risk was identified for the representative uses in fruiting vegetables. As regards the uses on ornamentals and in nursery stock, although they are not foodstuff, a consumer risk cannot be excluded considering the uptake of residues in the succeeding crops. In addition, the consumer intake via groundwater could not be finalised for M14 and M13 since no toxicological reference values were available.

The data available on environmental fate and behaviour are sufficient to carry out the required environmental exposure assessments at EU level for the representative uses. For the representative

uses, the 80th percentile annual average recharge concentrations leaving the top 1 m soil layer were estimated to be higher than 0.1 μg/L for metabolites M01, M02, M13, and M14. A groundwater monitoring study performed in Greece showed that the potential for groundwater exposure from the representative uses by fenamiphos was low for fenamiphos and its metabolites in the geoclimatic situations represented by the regions in Greece.

In the area of ecotoxicology, a high risk was concluded for soil organisms from metabolite M01. The risk to soil organisms from M14 and M13 could not be finalised with the available data. These two points are relevant in cases where the soil is removed and used outside and/or the greenhouse structure is removed shortly after application. EFSA notes a low risk to soil organisms from metabolites M01, M13 and M14 would be concluded only if mitigation measures are used to prevent exposure to the soil. A low risk to all other groups of non-target organisms was concluded.

Table of contents

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 Greece and co-RMS Cyprus received an application from AMVAC Netherlands B.V. for the renewal of approval of the active substance fenamiphos. Complying with Article 8 of the Regulation, the RMS checked the completeness of the dossier and informed the applicant, the co-RMS (Cyprus), the European Commission and EFSA about the admissibility.

The RMS provided its initial evaluation of the dossier on fenamiphos in the RAR, which was received by EFSA on 2 October 2017 (Greece, 2017).

In accordance with Article 12 of the Regulation, EFSA distributed the RAR to the Member States and the applicant, AMVAC Netherlands B.V., for consultation and comments on 21 December 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 February 2018. At the same time, the collated comments were forwarded to the RMS for compilation and evaluation in the format of a reporting table. The applicant was invited to respond to the comments in column 3 of the reporting table. The comments and the applicant's response were evaluated by the RMS in column 3.

The need for expert consultation and the necessity for additional information to be submitted by the applicant in accordance with Article 13(3) of the Regulation were considered in a telephone conference between EFSA and the RMS on 13 April 2018. On the basis of the comments received, the applicant's response to the comments and the RMS's evaluation thereof, it was concluded that additional information should be requested from the applicant, and that EFSA should conduct an expert consultation in the areas of mammalian toxicology 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 November 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 fenamiphos as a nematicide by drip irrigation in permanent greenhouse fruiting vegetables (i.e. tomato, aubergine, cucumber, pepper and courgette), herbaceous ornamentals and in nursery stock, in Southern Europe only, as proposed by the applicant. In accordance with Article 12(2) of Regulation (EC) No 1107/2009, risk mitigation options identified in the RAR and considered during the peer

[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.

review are presented in the conclusion. 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 tables (13 April 2018);
- the evaluation tables (6 December 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 (Greece, 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 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

Fenamiphos is the ISO common name for (*RS*)-(ethyl 4-methylthio-*m*-tolyl isopropylphosphoramidate) (IUPAC).

The representative formulated product for the evaluation was 'Nemacur CS 240', a capsule suspension (CS) containing 240 g/L of fenamiphos.

The representative uses evaluated were drip irrigation for the control of soil-dwelling nematodes, both endo- and ectoparasites in permanent greenhouse fruiting vegetables (i.e. tomato, aubergine, cucumber, pepper and courgette), in herbaceous ornamentals and in nursery stock (both perennial and herbaceous species), in Southern Europe only. Full details of the good agricultural practices (GAPs) can be found in the list of end points in Appendix A.

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

A data gap for screening of biological activity of metabolites fenamiphos-sulfone-phenol (M13) and fenamiphos-sulfone-anisole (M14) for all representative uses except for geoclimatic conditions of monitoring regions in Greece was identified (see Table 2).

A data gap has been identified for a search of the scientific peer-reviewed open literature on relevant metabolites fenamiphos-sulfoxide-phenol (M12), fenamiphos-sulfone-phenol (M13) and fenamiphos-sulfone-anisole (M14), dealing with side effects on the environment and non-target species and published within the 10 years before the date of submission of the dossier, to be conducted and reported in accordance with EFSA guidance on the submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009 (EFSA, 2011).

The active substance is a racemic compound and the methods of analysis used were not capable of quantifying the stereoisomers separately. Therefore, no information is available if they might degrade or otherwise transform at different rates in plants, animals and environmental matrices. This is discussed further in the individual sections.

Conclusions of the evaluation

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

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

The reference specification for fenamiphos was supported by batch data from industrial plant production and quality control data. The proposed minimum purity of the technical material is 940 g/kg. The proposed specification is supported by toxicological assessment (see Section 2). However, it should be noted that based on the data of the renewal procedure higher minimum purity of the active substance and lower maximum levels for some of the impurities could be set. There is no FAO specification available for fenamiphos.

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

Adequate methods are available for the generation of data required for the risk assessment. Methods of analysis are available for the determination of the active substance and the respective impurity in the technical material. Validated methods are available for determination of total and free (non-encapsulated) active substance in the representative formulation.

The components of the residue definition (fenamiphos, fenamiphos-sulfoxide (M01) and fenamiphos-sulfone (M02), expressed as fenamiphos) in plant commodities with high water content can be monitored by high-performance liquid chromatography with tandem mass spectrometry (HPLC–MS/MS) with limits of quantification (LOQs) of 0.01 mg/kg (fenamiphos eq.). A data gap for validation of the method in the other commodities was identified. An analytical method for food of animal origin is not required due to the fact that no residue definition is proposed.

The residue definition for monitoring in soil is open for M01, M13 and M14; as a consequence, monitoring methods might be required if the metabolites are included in the residue definition.

The components of the residue definition (fenamiphos, M01 and M02) in groundwater can be monitored by liquid chromatography with tandem mass spectrometry (LC–MS/MS) with LOQs of 0.1 μg/L. It should be noted that the residue definition for monitoring in groundwater is open for M14, as a consequence additional validation data (independent laboratory validation (ILV) for M14) might be required if the metabolite is included in the residue definition. Fenamiphos residues in surface water can be analysed by HPLC–MS/MS with a LOQ of 0.1 μg/L; however, a confirmatory method was not provided (data gap). The liquid chromatography with ultraviolet detection (LC-UV) method exists for monitoring of fenamiphos residues in air with a LOQ of 0.5 $\mu g/m^3$. It should be noted that the LOQ is not in compliance with the acceptable operator exposure level (AOEL); therefore, a data gap for additional validation data for the submitted method or a new method with a LOQ in compliance with the requirements for the operators, workers, residents and bystanders risk assessment was identified.

The LC–MS/MS method can be used for monitoring of fenamiphos, M01 and M02 converting them to M02 in body fluids and tissues with LOQs of 0.05 mg/L (fenamiphos eq.) and 0.1 mg/kg (fenamiphos eq.), respectively. However, residue definition for monitoring in body fluids and tissues was concluded as fenamiphos-phenol (M11), M13 and M12 (see Section 2); therefore, a data gap for monitoring method for these metabolites in body fluids and tissues was identified.

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), Guidance on dermal absorption (EFSA PPR Panel, 2012) and Guidance on the Application of the CLP Criteria (ECHA, 2017).

Fenamiphos was discussed at the Pesticides Peer Review Experts' Meeting 182 in September 2018.

Characterisation of the reference technical specification was supported through the evaluation of the composition of the batches used in the toxicology studies and through the *in silico*, i.e. quantitative structure–activity relationship (QSAR) evaluation, and weight of evidence, for the impurities quoted in the old and newly proposed technical specification but not present in the batches used for the conduction of the genotoxicity assays. Based on the assessment of the available data and weight of evidence, the non-toxicological relevance of the individual impurities was considered addressed. The analytical methods used in the toxicological studies were considered fit-for-purpose for the most relevant studies.

In vitro and *in vivo* absorption, distribution, metabolism and elimination (ADME) studies concordantly indicate that fenamiphos is rapidly cleared and nearly completely metabolised with renal excretion representing the main route of elimination. For the setting of the oral absorption value, total radioactivity is taken into account since the systemic effects based on which the reference values are

set, are due to either the active substance itself and/or its metabolites. As at 24 h more that 92% of the recovered total radioactivity was excreted in urine, the oral absorption value is set at 100%. There is no indication of accumulation of fenamiphos based on the available data. The ADME characteristics of fenamiphos, namely rapid and extensive metabolism and rapid clearance, indicate that the fenamiphos-phenols (methylthiometacresol (MTMC) derivatives, M11, M12, M13) should be considered for biomonitoring as they represent 80–96% of the recovered radioactivity. *In vitro* interspecies hepatic metabolism studies were not conducted with fenamiphos (data gap), leading to an issue not finalised.

Fenamiphos is considered very toxic after acute oral, dermal and inhalation exposure. It is additionally considered irritating to eyes but does not possess skin irritation or skin sensitisation properties and is not showing a phototoxic potential. The harmonised classification of fenamiphos, according to Regulation (EC) No 1272/2008, is acute oral H300; acute dermal H310; acute inhalation H330 and eye irritation H319.[3]

The main effect following short-term repeated oral, dermal and inhalation administration of fenamiphos was the inhibition of cholinesterase (ChE) activity, which at higher dose levels was leading to endogenous cholinergic overstimulation resulting in typical cholinergic symptoms. Erythrocyte ChE inhibition was in all studies the toxicologically most relevant effect. The dog was considered the most sensitive species and the no observed adverse effect level (NOAEL) of 0.083 mg/kg body weight (bw) per day (1-year dog study), based on erythrocyte ChE inhibition, was used to set the acceptable daily intake (ADI) and the AOEL.

Positive results for clastogenicity were observed in the chromosomal aberration assay in human lymphocytes. Fenamiphos was however negative in all the *in vivo* studies (dominant lethal test for germ cell chromosomal and dominant gene mutations and two micronucleus studies) and based on the available *in vitro* and *in vivo* tests, fenamiphos was considered not genotoxic.

Fenamiphos was not considered carcinogenic. Erythrocyte ChE inhibition was considered the most appropriate toxicological endpoint for hazard identification; as this parameter was not evaluated in the mouse study, the NOAEL value for systemic toxicity was only derived from the study conducted in rat.

Reproductive toxicity of fenamiphos was assessed in a two-generation reproductive toxicity study in rat and in the embryo foetal, teratogenicity studies conducted in rat and rabbit. In the rat two-generation study no evidence of reproductive toxicity was observed. The NOAEL for parental effect was set at 0.17 mg/kg bw per day based on erythrocyte acetylcholinesterase (AChE) inhibition and decreased body weight gain while the reproductive NOAEL was set at 2.8 mg/kg per day. The NOAEL for offspring was set at 0.64 mg/kg bw per day based on decrease in pup weight and erythrocyte AChE inhibition. As these effects were confined to lactation period, classification with H362 (may cause harm to breast-fed children) is proposed.[4] During the former peer review, this effect was considered for setting the NOAEL for the offspring but it was however not discussed and proposed for classification (neither at RAC level).

In the rat developmental study, the NOAEL for maternal toxicity was set at 0.25 mg/kg bw per day based on erythrocyte AChE inhibition at day 16 and the developmental NOAEL was set at 0.85 mg/kg bw per day based on variations of the hyoid body or arch. In rabbit, the developmental and maternal NOAEL was set at 0.1 mg/kg bw per day based on skeletal findings in the foetuses and decrease in body weight gain and clinical signs in the parent. This dose was however not considered suitable for setting the acute reference dose (ARfD) as the onset of the effects from which the NOAEL was derived was not considered acute.

Fenamiphos is neurotoxic with the lowest NOAEL set in the dog at 0.25 mg/kg bw based on erythrocyte ChE inhibition and clinical signs at higher doses. This study was used to derive the ARfD and the acute acceptable operator exposure level (AAOEL) of fenamiphos. The relevant NOAEL for short term neurotoxicity is 0.06 mg/kg bw per day based on clinical signs and inhibition of brain cholinesterase in the 15-week rat neurotoxicity study. Fenamiphos has no potential to induce delayed neuropathy and there were no developmental neurotoxicity (DNT) effects in a DNT study conducted in rat. In this study, the NOAEL for maternal toxicity was set at 0.5 mg/kg bw per day, based on decreased erythrocyte ChE activity at lactation day (LD) 21 at 2.1 mg/kg bw per day. The NOAEL for

[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

[4] It should be noted that harmonised classification and labelling is formally proposed and decided in accordance with Regulation (EC) No 1272/2008.

offspring toxicity was set at 2.1 mg/kg bw per day, based on decreased erythrocyte activity in males and females at post-natal day (PND) 21 at 10.3 mg/kg bw per day.

EFSA considers that an endocrine disruptor (ED) assessment in line with current guidance for the identification of endocrine disruptors in the context of Regulation (EU) No 1107/2009 is not scientifically necessary for fenamiphos (ECHA and EFSA, 2018). In all the studies conducted with fenamiphos, the NOAEL, lowest observable adverse effect level (LOAEL) and the maximum tolerated dose (MTD) were based on erythrocyte ChE inhibition and clinical signs at higher doses. The overall dose–response pattern for cholinergic overstimulation indicates that fenamiphos is a potent ChE inhibitor, and this is practically limiting the possibility of exploring additional target organ/systems.

Fenamiphos was not showing any immunotoxic effect in a 4-week immunotoxicity study conducted in rat.

Based on the similarity in the toxicological profile and NOAEL between the 1-year and 2-year dog studies, the experts agreed to set an overall NOAEL for dogs (most sensitive species for AChE activity) of 0.083 mg/kg bw per day as the point of departure for setting the ADI, established at 0.00083 mg/kg bw per day based on an uncertainty factor (UF) of 100. The same ADI was established in the previous assessment.

The ARfD was set at 0.0025 mg/kg bw based on the acute oral neurotoxicity study in dogs with a NOAEL of 0.25 mg/kg bw, which was based on erythrocyte ChE inhibition, clinical signs and application of an UF of 100. The same ARfD was established in the previous assessment.

The AOEL was set at 0.0008 mg/kg bw per day on the same basis as for the ADI setting (0.00083 mg/kg bw per day with an UF of 100 with no correction for oral absorption). The same AOEL was established in the previous assessment.

The experts agreed to establish an AAOEL at 0.0025 mg/kg bw per day on the same basis as the ARfD with no correction for oral absorption (i.e. 0.0025 mg/kg bw based on the acute oral neurotoxicity study in dogs with a NOAEL of 0.25 mg/kg bw based on erythrocyte ChE inhibition and clinical signs, with an UF of 100).

The representative formulation 'Nemacur CS 240' is a capsule suspension, containing a nominal concentration of 240 g/L of fenamiphos for which *in vitro* dermal absorption studies using human skin have been conducted. The absorption values of the concentrate formulation were 1% while it was 8% for the diluted one (12 g/L). For the representative uses in drip irrigation in permanent greenhouses, the risk assessment of fenamiphos, based on a field study, indicates that the use of personal protective equipment (PPE) is necessary to avoid exceedance of the AOEL and AAOEL for operators. Finally, based on the calculations of the exposure of a worker from the direct contact with treated soil, the total systemic exposure is below the AOEL value of fenamiphos, even when no PPE is worn, assuming adequate work clothing (EFSA model; EFSA, 2014b). During drip irrigation, the formulation is released into the ground by hoses, which are placed directly aside the plant stem. Therefore, bystander and resident exposure during application is considered to be negligible.

It is noted that the relative toxicity and possible preferential metabolism/degradation of the enantiomers present in animals, plants and the environment was not investigated; however, considering the high margin between worker exposure and the AOEL, it is considered unlikely that the AOEL would be exceeded even if a complete shift would occur after application to a potentially more toxic enantiomer.

Toxicological data were submitted for some metabolites found in groundwater or as residues (crops or livestock). The metabolites M11, M12 and M13 covered the large majority of the recovered radioactivity in ADME studies and they lack by ester cleavage the toxophore responsible for the pesticidal and toxicological mode of action. They are clearly less toxic than the parent active substance as demonstrated by the higher LD_{50} (above 1,000 mg/kg bw for all of them). Their genotoxicity profiles were also considered sufficiently characterised by the studies conducted with the parent active substance as they are major metabolites in rat. The metabolite M13 (as groundwater metabolite) is not relevant based on hazard screening but appropriate data for setting the ADI and conducting a consumer risk assessment are lacking (metabolite is expected to be of lower toxicity than the parent), leading to a data gap and an issue not finalised.[5] EFSA considers that a similar argumentation, based on structural similarity, can be used for the evaluation of the groundwater metabolite M14, for which no data are available, leading also to a data gap and an issue not finalised. Additional metabolites were detected in low amount in the urine or in *in vitro* metabolism studies (M01 and M02). These

[5] The use of the reference values set for the parent could be considered as worst case scenario; however, the worst-case scenario will result in exceeding the threshold for concern for groundwater metabolites.

metabolites retain the toxophore moiety and are similar/more toxic than fenamiphos based on LD_{50} values. Genotoxicity assessment for M01 and M02 was considered incomplete for the endpoints aneugenicity/clastogenicity; this is because fenamiphos was positive *in vitro* for the endpoint clastogenicity and these metabolites are structurally very similar to the parent active substance. Reference values for the parent should be applied in the risk assessment of M01 and M02 provided that the genotoxic potential (aneugenicity/clastogenicity) is excluded (data gap). Finally, these metabolites are already considered toxicologically relevant based on the available data.

Metabolite des-isopropylamino fenamiphos sulfoxide (M09) was found in rotational crops. An acute oral toxicity test along with an Ames test are available showing that M09 is less or at least equally toxic than the parent compound and does not induce point mutations. However, genotoxic characterisation for the end points aneugenicity/clastogenicity is lacking. The toxicological reference values set for the parent should be applied to M09, providing that the genotoxic potential (aneugenicity/clastogenicity) is excluded (data gap).

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).

Fenamiphos was discussed at the Pesticides Peer Review Experts' Meeting 184 in September 2018.

The metabolism of fenamiphos in primary crops was investigated in fruit crops (tomatoes), miscellaneous crops (pineapples), root crops (carrots), leafy crops (tobacco, cabbage) and pulses and oilseeds (beans) following several modes of application (i.e. soil and foliar treatments, stem injection) with appropriate labelling of the parent molecule. Although shortcomings were noted, such as non-specified storage conditions of the residue samples in the study reports and metabolites' identification occurred mainly in the chloroform extract, all the metabolism studies were considered as sufficiently reliable to depict the metabolic pattern of fenamiphos in all crop groups. Throughout all the studies the predominant compounds found were M01 (up to 90% total radioactive residues (TRRs)) and M02 (up to 24% TRR), while parent fenamiphos accounted only for maximum 9% TRRs in tomato fruits. M12 and M13 (free and/or conjugates) were also identified mainly in cabbage leaves following soil application. Based on the overall metabolism studies, the **monitoring residue definition** is proposed as 'sum of fenamiphos, M01 and M02 expressed as fenamiphos'. For risk assessment, the inclusion of M12 and M13 in the residue definition was also considered. However, since these compounds are of lower acute toxicity and show a different mode of action compared to the parent compound (see Section 2), the majority of the experts was not in favour to include these metabolites in the residue definition for risk assessment. Since for M01 and M02, the same toxicological reference values as for the parent can be used, the same residue definition as for monitoring is proposed also **for risk assessment**, is 'sum of fenamiphos, M01 and M02 expressed as fenamiphos'. However, additional toxicological data to exclude the genotoxicity of M01 and M02 are requested (see data gap in Section 2), and pending their evaluation the expression of the risk assessment residue definition might be reconsidered. The metabolism studies are available for all crop categories and the metabolic pattern was similar; the derived residue definition covers all crop groups following soil applications.

Confined rotational metabolism studies were conducted at dose rate from 6.7 kg a.s./ha to 7.6 kg a.s./ha in roots (sugar beet, red beet), leafy crops, mustard, Swiss chards) and cereals (wheat, oats) following soya bean treatments. In the edible parts of the rotational crops, the major compounds found were M01 (max. 28% TRRs in Swiss chards), M02 (max. 20% TRRs in Swiss chards), while M12 and M13 (free and/or conjugates) were also recovered in significant levels, max. 10% TRRs in red beet roots and 25% TRRs in Swiss chards, respectively. In one study M09 was also analysed and found at significant proportions/concentrations in Swiss chard (14–37% TRR) at all plant-back intervals (PBIs), and in tops beet roots (5–13% TRRs). One additional metabolism study on bare soil at a dose rate of 10 kg a.s./ha conducted specifically with tomatoes planted after 7 and 60 days ageing of soil was also available. The residue levels in tomato fruits in this study were significant, after ageing of soil for 7 days, M01 was found up to 31% TRRs (0.028 mg/kg), M02 up to 11% (0.01 mg/kg) TRRs, M12 up to 25% TRRs and M13 up to 44% TRRs, and hence, there is a clear indication of the uptake of residues in the following crops. Considering the occurrence of M01, M02 and M09 observed in the rotational crop metabolism studies, the soil persistence of M01 ($DT_{90:}$ max. 485 days) and M02 (DT_{90}

max. 282 days) (see Section 4) and the lack of sufficient toxicity data on M09 (see data gap in Section 2), additional data on the magnitude of residues in rotational crops is necessary. Therefore additional field trials on leafy crops analysing for fenamiphos, M01, M02 and M09 at all PBIs and covering the predicted environmental concentration in soil (PEC_{soil}) are requested (data gap). Pending the outcome on the evaluation of the additional field rotational trials, the toxicological evaluation of M09, the same residue definitions as for primary crops are applicable also for rotational crops. However, the risk assessment residue definition for rotational crops is provisional.

Three outdoor rotational field trials conducted in the USA in cereals (wheat, sorghum), roots (turnip), leafy crops (spinach, mustard) grown in rotation with soya bean following soil application of 6.7 kg a.s./ha and analysed for fenamiphos, M01 and M02 were submitted. Although the residue levels decreased from the first to the second PBI (i.e. in spinach from 0.24 mg/kg to < 0.01 mg/kg for fenamiphos, from 0.5 mg/kg to 0.14 mg/kg for M01 and from 0.28 mg/kg to 0.12 mg/kg for M02), the residues remained significant in food crop parts. However, the available trials were conducted outdoor in different climatic conditions compared with the representative GAPs, and thus they were not considered fully reliable.

Sufficient field trials in fruiting vegetables analysing the residues in accordance with the agreed residue definitions for monitoring and risk assessment were submitted in tomatoes, aubergines peppers, cucumbers and courgettes. It was noted however that some trials in tomatoes, peppers and courgettes were conducted at a later growth stage, i.e. at a BBCH GS 62 and 74, respectively compared to the critical BBCH GS 61 as reported in the representative uses for tomatoes and peppers; or at a BBCH 16-18 instead of BBCH 15 for the residue trials on courgettes. The acceptability of these trials was therefore questionable. Since flowering and fruit ripening may occur simultaneously in the treated field, it was agreed to consider all residue trials with a preharvest interval (PHI) of 60 days as acceptable. All the trials are supported by a validated analytical method. Acceptable storage stability of the residues was demonstrated for garlic and asparagus belonging to the high water content commodities. Nevertheless, for the representative use on fruiting vegetables additional storage stability data on a crop representative of the fruiting vegetables are requested to comply with the current recommendations (data gap).

Under the standard hydrolysis conditions representative of food processing, fenamiphos residues were found to be stable. Although no specific hydrolysis studies were submitted for M01 and M02, no degradation is expected under processing, since fenamiphos, which has similar chemical structure, is stable. Since the residue levels were higher than 0.1 mg/kg in fruiting vegetable crops and the theoretical maximum daily intake (TMDI) and the international estimated short-term intake (IESTI) exceeded 10% of the ADI and ARfD, respectively, processing trials are necessary to derive reliable processing factors (data gap).

Livestock metabolism studies including fish were not available and they are also not needed since none of the representative uses are fed to livestock.

The consumer risk assessment has been conducted for tomatoes, aubergines, peppers, cucumbers and courgettes by using the EFSA PRIMo rev.2A model. There is an acute intake risk identified for all fruiting vegetables assessed under the representative uses, since the IESTI exceeded the ARfD as follows: 1,108% (peppers, DE adult), 538% (cucumbers, NL adult), 512% (tomatoes, BE adult), 427% (courgettes, UK toddler), 220% (aubergines, UK child), 150% gherkins (NL adult). For the chronic intake consumer exposure, if the calculated MRLs resulting from the available residue dataset submitted for the renewal process are used in the exposure assessment, the maximum TMDI would account for 172% of the ADI (tomatoes, WHO Cluster diet B). Nevertheless, the TMDI associated to the existing MRLs accounted for 11% of the ADI. In addition, although herbaceous ornamentals and nursery stock are not foodstuff, they could be grown in rotation with other food crops. Thus, based on rotational metabolism studies in fruiting vegetables conducted at 1N application rate, when compared with the annual application rate from the representative GAP in ornamentals and nursery stock and also in view of the very low toxicological reference values of fenamiphos, an acute consumer risk cannot be excluded.

Although sufficient residue trials were available for all representative uses in fruiting vegetables, no MRL could be proposed due to the acute consumer risk intake.

As regards the consumer intake trough drinking water for M01 and M02 expressed as fenamiphos, it is estimated for adults as 3.3% of the ADI, child for 9.98% of the ADI and infants for 14.9% of the ADI. For M13 and M14, the consumer risk assessment could not be finalised since not sufficient toxicological data are available (see Sections 2 and 4). The overall consumer risk assessment for food and groundwater should be regarded as provisional since the risk assessment residue definition for

rotational crops is provisional and pending upon the outcome of the toxicological evaluation of the relevant metabolites.

Currently, no change in the residue definitions derived in the framework of the MRL review under Article 12 of Regulation (EC) No 396/2005 (EFSA, 2009a) are proposed and the toxicological reference values are not lowered compared to the ones proposed during the first approval of the substance. Therefore, the Art. 12 MRL review does not need to be revised for the time being.

As regards the maximum levels of the residues in pollen and honeybee products, since the representative uses are all within permanent greenhouse, no visiting by the bees is expected.

4. Environmental fate and behaviour

The rates of dissipation and degradation in the environmental matrices investigated were estimated using FOCUS (2006) kinetics guidance. In soil laboratory incubations under aerobic conditions in the dark, fenamiphos exhibited very low persistence, forming the major (> 10% applied radioactivity (AR)) metabolites M01 (max. 77.2% AR), which exhibited low to high persistence, metabolite M02 (max. 29.3% AR), which exhibited low to medium persistence, metabolite M12 (max. 6.5% AR), which exhibited low to moderate persistence, and metabolite M13 (max. 25.1% AR), which exhibited moderate to high persistence. In addition, metabolite M14 (max. 8.2% AR) exceeded 5% AR in at least two consecutive sampling dates in the degradation experiments; therefore it was included in the present assessment. M14 exhibited medium to high persistence in soil. The metabolites M01 and M02 retain the chiral phosphorous atom and whether there was any preferential transformation of their stereoisomers is not known. Mineralisation of the phenyl ring ^{14}C radiolabel to carbon dioxide accounted for 23–52.1% AR after 120 days. The formation of non-extractable residues (not extracted by acetonitrile/water) for this radiolabel accounted for 34.7% AR after 120 days. Anaerobic conditions and soil photolysis are not considered relevant for the representative uses. Fenamiphos exhibited very high to medium mobility in soil. Metabolites M01 and M02 exhibited very high to medium mobility in soil. M12 and M13 exhibited very high soil mobility, and M14 exhibited high soil mobility. It was concluded that the adsorption of fenamiphos and its metabolites was not pH dependent. The available field dissipation study was concluded to provide information on the fate of fenamiphos under field conditions. However, it was concluded that field dissipation studies do not reflect greenhouse environmental conditions, and then the degradation of fenamiphos applied through drip irrigation in greenhouses is represented by laboratory studies.

In laboratory incubations in dark aerobic natural sediment water systems, fenamiphos exhibited low to high persistence, forming the major metabolites M01 (max. 13.7% AR in water and 16.8% AR in sediment) and M12 (max. 10.8% AR in water). The non-extractable sediment fraction was the major sink for the phenyl ring ^{14}C radiolabel, accounting for 17–41% AR at study end (100 days). Mineralisation of this radiolabel accounted for 2.4–14.3% AR at the end of the study. Irradiation of phenyl labelled fenamiphos in sterile aqueous photolysis experiment resulted in the formation of the major photodegradation products M01 (max. 17.3% AR) and fenamiphos-phenol-sulfonic acid (max. 18.6% AR). Surface water and sediment exposure assessments (PEC calculations) were not carried out as considering the representative uses (permanent greenhouse, drip irrigation, southern Europe), it was concluded that exposure to surface water and sediment via drift, run-off/erosion and drainage is not expected based on assessment provided by the applicant for these uses.

The necessary groundwater exposure assessments were carried out following EFSA guidance on emission from protected crops (EFSA, 2014a) using the FOCUS Piacenza scenario for tomatoes modified considering different weather and crop parameters and the model PEARL 4.4.4. The potential for groundwater exposure from the representative uses by fenamiphos above the parametric drinking water limit of 0.1 μg/L was concluded to be low for fenamiphos and metabolite M12 in this groundwater scenario. For the representative uses, the 80th percentile annual average recharge concentrations leaving the top 1 m soil layer were estimated to be higher than 0.1 μg/L for metabolites M01, M02, M13 (the latter exceeding also 0.75 μg/L) and M14 (exceeding also 10 μg/L). A groundwater monitoring study was performed in three vulnerable regions in Greece showing that the potential for groundwater exposure from the representative uses by fenamiphos above the parametric drinking water limit of 0.1 μg/L was concluded to be low for fenamiphos and metabolites M01, M02, M12, M13 and M14 in the geoclimatic situations that are represented by the regions in Greece.

As reported in the EFSA guidance on emission from protected crops (EFSA, 2014a), an assessment of soil exposure as it was for open field is required for persistent substances (DT_{90} > 1 year) to account for possible change of destination of the soil within the structure in the longer term (e.g. if the

soil is removed and used outside and/or the structure is removed). Therefore, an assessment was triggered for metabolites M01, M13 and M14. However, EFSA notes that exposure to soil would be expected in case the soil is removed and used outside and/or the structure is removed within 12 months from the last application; otherwise, if the soil is removed and used outside and/or the structure is removed after 12 months from the last application exposure to soil would not be expected (see Section 5).

Based on the chemical structure of the active substance, the applicant provided information to address the effect of water treatment processes on the nature of the residues that might be present in groundwater, when groundwater is abstracted for drinking water. The conclusion of this consideration was that neither fenamiphos nor any of its degradation products that trigger assessment (M01, M02, M12, M13 and M14) would be expected to undergo any substantial transformation due to oxidation at the disinfection stage of usual water treatment processes.

The active substance is a racemic compound and the methods of analysis used were not capable of quantifying the stereoisomers separately. However, having knowledge of the stereoisomer characterisation, it would not change the conclusion considering the exposure.

The PEC in soil for metabolites M01, M13 and M14 over 20 cm, and groundwater covering the representative uses assessed can be found in Appendix A of this conclusion.

5. Ecotoxicology

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

Toxicity data for non-target organisms were available in the dossier; however, with the exception of the toxicity data for aquatic organisms and bumblebees, the RMS did not evaluate the data. As the representative uses of fenamiphos are restricted to permanent greenhouses via drip irrigation, no exposure to terrestrial vertebrates, aquatic organisms, wild bees, non-target arthropods, non-target terrestrial plants and sewage treatment organisms is anticipated. Consequently, a low risk to these groups of non-target organisms is concluded.

Exposure to soil organisms from fenamiphos is also excluded and a low risk can be concluded. However, for the persistent metabolites, M01, M13 and M14, exposure to soil is expected in cases where the soil is removed and used outside and/or the structure is removed within 12 months after application. Data demonstrating the toxicity of M01 and M13 to *Folsomia candida* were included in the dossier and in the previous EFSA conclusion for fenamiphos (EFSA, 2006). EFSA checked the reliability of the study and considered that the endpoints are valid and reliable. EFSA performed a risk assessment, using the available no observed effect concentration (NOEC) values, which indicated a high risk to soil macroorganisms from metabolite M01 (data gap) but a low risk was indicated for metabolite M13. It was noted that no EC_{10} values were available in the studies performed with *F. candida* which is a requirement of EU Regulation 283/2013[6]; however, as a high risk was already indicated, no further data gap was identified. No suitable data were available demonstrating the toxicity of M01, M13 and M14 to earthworms, *Hypoaspis aculeifer* and soil microorganisms (data gap). Furthermore, no suitable data were available demonstrating the toxicity of M14 to *F. candida* (data gap). However, as noted by EFSA in Section 4, exposure to soil would not be expected in cases where the soil is removed and used outside and/or the structure is removed after 12 months from the last application (see Section 4). In these circumstances a low risk to soil organisms from persistent soil metabolites would be concluded.

Studies investigating the potential effect of fenamiphos to bumble bee pollinators introduced to greenhouses were available. However, these studies were not presented in sufficient detail to verify a low risk. Therefore, a risk to pollinators introduced to glasshouses cannot be excluded.

No data and assessment investigating the potential of fenamiphos to have endocrine disrupting properties to non-target organisms, according to the ECHA and EFSA guidance (2018), were available.

However, considering that the only representative use of fenamiphos is via drip irrigation in permanent greenhouses, for which it was demonstrated that exposure to non-target organisms is not expected, no further data are considered necessary.

[6] Commission Regulation (EU) No 283/2013 of 1 March 2013 setting out the data requirements for active substances, in accordance with 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 93, 3.4.2013, p. 1–84.

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
Fenamiphos	Very low persistence Biphasic kinetics DT_{50} 0.15–0.62 days (DT_{90} 1.3–7.1 days; laboratory conditions at 20°C, pF2 – 40% MWHC soil moisture)	No risk assessment performed owing to no exposure anticipated for the representative use
Fenamiphos-sulfoxide (M01)	Low to high persistence Biphasic kinetics DT_{50} 3.5–22.6 days (DT_{90} 18.2–485.2 days; laboratory conditions at 20°C, pF2 – 40% MWHC soil moisture)	High risk to soil macroorganisms. Data gap for toxicity data for earthworms, and *Hypoaspis aculeifer* and soil microorganisms. Relevant only in situations where the soil is removed from the greenhouse and used outside and/or the greenhouse structure is removed within 12 months from the last application
Fenamiphos-sulfone (M02)	Low to medium persistence Single first-order and biphasic kinetics DT_{50} 1.5–84.8 days (DT_{90} 5.2–282 days; laboratory conditions at 20°C, pF2 – 40% MWHC soil moisture)	No risk assessment performed owing to no exposure anticipated for the representative use
Fenamiphos-sulfoxide-phenol (M12)	Low to moderate persistence Single first-order DT_{50} 2.5–29.4 days (DT_{90} 8.5–97.8 days; laboratory conditions at 20°C, pF2 – 40% MWHC soil moisture)	No risk assessment performed owing to no exposure anticipated for the representative use
Fenamiphos-sulfone-phenol (M13)	Moderate to high persistence Single first-order and biphasic kinetics DT_{50} 12.4–58.3 days (DT_{90} 41.2–> 1,000 days; laboratory conditions at 20°C, pF2 – 40% MWHC soil moisture)	Low risk to soil macroorganisms. Data gap for toxicity data for earthworms, and *Hypoaspis aculeifer* and soil microorganisms Relevant only in situations where the soil is removed from the greenhouse and used outside and/or the greenhouse structure is removed within 12 months from the last application
Fenamiphos-sulfone-anisole (M14)	Medium to high persistence Single first-order and biphasic kinetics DT_{50} 58.4–184 days (DT_{90} 315–612 days; laboratory conditions at 20°C, pF2 – 40% MWHC soil moisture)	Data gap for toxicity data for earthworms, soil macroorganisms and soil microorganisms. Relevant only in situations where the soil is removed from the greenhouse and used outside and/or the greenhouse structure is removed within 12 months from the last application

DT_{50}: period required for 50% dissipation (define method of estimation); DT_{90}: period required for 90% dissipation (define method of estimation); MWHC: maximum water-holding capacity; pF2: pF value of 2 (suction pressure that defines field capacity soil moisture).

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
Fenamiphos	Very high to medium mobility K_{Foc} 44–241 mL/g	No	Yes	Yes
Fenamiphos-sulfoxide (M01)	Very high to medium mobility K_{Foc} 27–225 mL/g	Spring application at 10 kg/ha (**0.14–0.72** µg/L) Spring application at 4 kg/ha (0.03–**0.16** µg/L) Monitoring in Greece (0.065 µg/L)	Data not available; not triggered for geoclimatic conditions of monitoring regions in Greece	Yes (insufficient data to exclude genotoxicity – data gap for clastogenicity/aneugenicity)
Fenamiphos-sulfone (M02)	Very high to medium mobility K_{Foc} 32–311 mL/g	Spring application at 10 kg/ha (0.03–**0.16** µg/L) Monitoring in Greece (not detected)	Data not available; not triggered for geoclimatic conditions of monitoring regions in Greece	Yes (insufficient data to exclude genotoxicity – data gap for clastogenicity/aneugenicity).
Fenamiphos-sulfoxide-phenol (M12)	Very high mobility K_{Foc} 20–22 mL/g	No Monitoring in Greece (0.040 µg/L)	Data not available; not triggered for geoclimatic conditions of monitoring regions in Greece	Assessment not triggered
Fenamiphos-sulfone-phenol (M13)	Very high mobility K_{Foc} 32–50 mL/g	Spring application at 10 kg/ha (**0.14–1.0** µg/L) Spring application at 4 kg/ha (0.02–**0.16** µg/L) Monitoring in Greece (0.090 µg/L)	Data not available; not triggered for geoclimatic conditions of monitoring regions in Greece	Assessment triggered except for geoclimatic conditions of monitoring regions in Greece Metabolite is not relevant based on hazard screening but appropriate data for setting the ADI and conducting consumer risk assessment is lacking (data gap) (metabolite is expected to be of lower toxicity than the parent)
Fenamiphos-sulfone-anisole (M14)	High mobility K_{Foc} 54–76 mL/g	Spring application at 10 kg/ha (**141.7–259.4** µg/L) Spring application at 4 kg/ha (**35.3–66.2** µg/L)Monitoring in Greece (0.045 µg/L)	Data not available; not triggered for geoclimatic conditions of monitoring regions in Greece	Assessment triggered except for geoclimatic conditions of monitoring regions in Greece Metabolite is not relevant based on hazard screening but appropriate data for setting the ADI and conducting consumer risk assessment is lacking (data gap) (metabolite is expected to be of lower toxicity than the parent)

K_{Foc}: Freundlich organic carbon adsorption coefficient; ADI: acceptable daily intake.
(a): FOCUS scenarios or a relevant lysimeter.

Table 3: Surface water and sediment

Compound (name and/or code)	Ecotoxicology
No exposure expected.	

Table 4: Air

Compound (name and/or code)	Toxicology
Fenamiphos	Rat LC_{50} inhalation: 65–79 μg/L per 4 h (aerosol); classified as fatal if inhaled (**Acute Tox. 2; H330)**

LC_{50}: lethal concentration, 50%.

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 search of the scientific peer-reviewed open literature on relevant metabolites M12, M13 and M14, dealing with side effects the environment and non-target species and published within the 10 years before the date of submission of the dossier, to be conducted and reported in accordance with EFSA guidance on the submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009 (EFSA, 2011; relevant for all representative uses evaluated).
- Screening for biological activity of metabolites M13 and M14 (relevant for all representative uses evaluated except for geoclimatic conditions of monitoring regions in Greece).
- Analytical methods for monitoring of the residue definition in dry, high acidic and high oil content commodities (relevant for all uses on dry, high acidic and high oil content commodities; see Section 1).
- A confirmatory method of the method for monitoring of fenamiphos residues in surface water (relevant for all representative uses evaluated; see Section 1).
- Additional validation data for the submitted monitoring method in air or a new method with a LOQ in compliance with the requirements for the operators, workers, residents and bystanders risk assessment (relevant for all representative uses evaluated; see Section 1).
- Analytical methods for monitoring of M11, M13 and M12 in body fluids and tissues (relevant for all representative uses evaluated; see Section 1).
- *In vitro* comparative metabolism study including the identification of rat, mouse, dog and human metabolites (Regulation (EC) No 283/2013) (relevant for all representative uses evaluated; see Section 2).
- Appropriate data for setting the ADI and conducting a consumer risk assessment for the groundwater metabolites M13 and M14 (relevant for the representative use of drip irrigation in greenhouses; see Section 2).
- Exclusion of genotoxicity (aneugenicity/clastogenicity) for the rotational crop metabolite M09 (relevant for all representative uses evaluated; see Section 2).
- Exclusion of genotoxicity (aneugenicity/clastogenicity) for the metabolites M01 and M02 (relevant for all representative uses evaluated; see Section 2).
- Sufficient rotational field trials on leafy crops analysing for fenamiphos, M01, M02 and M09 at all PBIs and covering the PECsoil (relevant for all representative uses evaluated; see Section 3).
- Sufficient processing trials to derive reliable processing factors (relevant for the representative uses on fruiting vegetables; see Section 3).
- Additional storage stability data on a crop representative of the fruiting vegetables to comply with the current recommendations (relevant for the representative uses on fruiting vegetables; see Section 3).
- Data to address the risk to earthworms, *H. aculeifer* and soil microorganisms from metabolites M01, M13 and M14. Data to also address the risks to *F. candida* from metabolite M14 (relevant for all representative uses evaluated in situations where the soil is removed from the greenhouse and used outside and/or the greenhouse structure is removed within 12 months from the last application; submission date proposed by the applicant: unknown; see Section 5).
- Further data are needed to address the high risk to *F. candida* from metabolite M01 (relevant for all representative uses evaluated in situations where the soil is removed from the greenhouse and used outside and/or the greenhouse structure is removed within 12 months from the last application; 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

- Operator should wear gloves and coverall to reduce exposure below the AOEL/AAOEL (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[7] and if the issue is of such importance that it could, when finalised, become a concern (which would also be listed as a critical area of concern if it is of relevance to all representative uses).

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 risk assessment to unique human metabolites could not be finalised whilst an *in vitro* comparative metabolism study was not submitted (see Section 2).
2) The consumer risk assessment through groundwater could not be finalised for M13 and M14 since toxicological information are not available (see Sections 2, 3 and 4).
3) The overall consumer risk assessment for food and groundwater is provisional since the data package for M01 and M02 on genotoxicity was incomplete and the expression of the risk assessment residue definition for primary crops is provisional. Moreover, the risk assessment residue definition in rotational crops is provisional (see Sections 2 and 3). It should be noted that even if the consumer risk assessment could not be finalised, an acute consumer risk was identified for all fruiting vegetables representative uses while for the ornamentals and nursery stock, they can be grown into rotation with food crops and therefore an acute consumer risk cannot be excluded.

9.2. Critical areas of concern

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

An issue is also listed as a critical area of concern if the assessment at a higher tier level could not be finalised due to lack of information, and if the assessment performed at 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 area of concern 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).

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

Table 5: Overview of concerns

Representative use		Tomato	Aubergine	Pepper	Cucumber	Courgette	Herbaceous ornamentals	Nursery stock
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	X[3(d)]	X[3(d)]	X[3(d)]	X[3(d)]	X[3(d)]		
	Assessment not finalised	X[2]	X[2]	X[2]	X[2]	X[2]	X[2,3(c)]	X[2,3(c)]
Risk to wild non-target terrestrial vertebrates	Risk identified							
	Assessment not finalised							
Risk to wild non-target terrestrial organisms other than vertebrates	Risk identified	X[(b)]	X[(b)]	X[(b)]	X[(b)]	X[(b)]	X[(b)]	X[(b)]
	Assessment not finalised							
Risk to aquatic organisms	Risk identified							
	Assessment not finalised							
Groundwater exposure to active substance	Legal parametric value breached							
	Assessment not finalised							
Groundwater exposure to metabolites	Legal parametric value breached	Yes: greenhouse scenario No: monitoring greenhouse in Greece	Yes: greenhouse scenario No: monitoring greenhouse in Greece	Yes: greenhouse scenario No: monitoring greenhouse in Greece	Yes: greenhouse scenario No: monitoring greenhouse in Greece	Yes: greenhouse scenario No: monitoring greenhouse in Greece	Yes: greenhouse scenario No: monitoring greenhouse in Greece	Yes: greenhouse scenario No: monitoring greenhouse in Greece
	Parametric value of 10 µg/L[(a)] breached							
	Assessment not finalised							

The superscript numbers relate to the numbered points indicated in Sections 9.1. Where there is no superscript number, see Sections 2–6 for further information.

(a): Value for non-relevant metabolites prescribed in SANCO/221/2000-rev. 10 final, European Commission, 2003.

(b): A high risk to soil organisms is indicated only in situations where the soil is removed from the greenhouse and used outside and/or the greenhouse structure is removed before 12 months from the last application. Consequentially, this is not considered as a critical area of concern.

(c): Assessment not finalised for rotational crops.

(d): Only a provisional risk assessment is performed; however, even considering the M01 and M02 as non-genotoxic, an acute consumer risk intake is already identified.

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Abbreviations

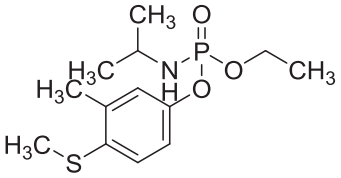
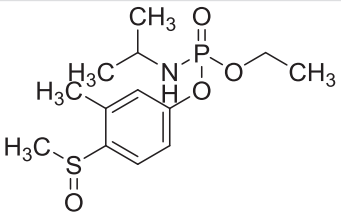
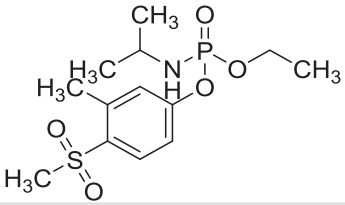
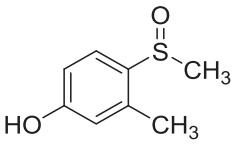
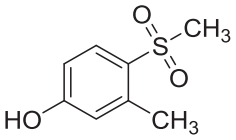
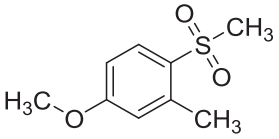
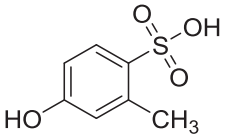
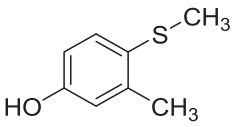
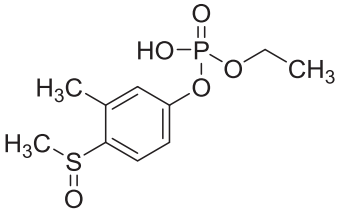
a.s.	active substance
AChE	acetylcholinesterase
ADE	actual dermal exposure
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism and elimination
AF	assessment factor
AAOEL	acute acceptable operator exposure level
AOEL	acceptable operator exposure level
AR	applied radioactivity
ARfD	acute reference dose
bw	body weight
ChE	cholinesterase
CLP	classification, labelling and packaging
CS	capsule suspension
DAR	draft assessment report
DNT	developmental neurotoxicity
DT_{50}	period required for 50% dissipation (define method of estimation)
DT_{90}	period required for 90% dissipation (define method of estimation)
EC_{10}	effective concentration, 10%
ECHA	European Chemicals Agency
ED	endocrine disruptor
EEC	European Economic Community
FOCUS	Forum for the Co-ordination of Pesticide Fate Models and their Use
GAP	Good Agricultural Practice
GS	growth stage
HPLC-MS/MS	high- performance liquid chromatography with tandem mass spectrometry
IESTI	international estimated short-term intake
ILV	independent laboratory validation
InChiKey	International Chemical Identifier Key.
ISO	International Organization for Standardization
IUPAC	International Union of Pure and Applied Chemistry

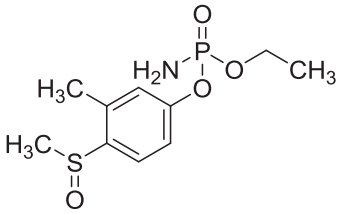
JMPR	Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues (Joint Meeting on Pesticide Residues)
K_{Foc}	Freundlich organic carbon adsorption coefficient
LC_{50}	lethal concentration, median
LC-MS/MS	liquid chromatography with tandem mass spectrometry
LC-UV	liquid chromatography with ultraviolet detector
LD	lactation day
LD_{50}	lethal dose, median; dosis letalis media
LOAEL	lowest observable adverse effect level
LOQ	limit of quantification
MRL	maximum residue level
MTD	maximum tolerated dose
MTMC	methylthiometacresol
MWHC	maximum water-holding capacity
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed 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
pF2	pF value of 2 (suction pressure that defines field capacity soil moisture)
PHI	pre-harvest interval
PND	post-natal day
PPE	personal protective equipment
QSAR	quantitative structure–activity relationship
RAC	regulatory acceptable concentration
RAR	Renewal Assessment Report
RMS	rapporteur Member State
SMILES	simplified molecular-input line-entry system
TMDI	theoretical maximum daily intake
TRR	total radioactive residue
UF	uncertainty factor
UV	ultraviolet
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.2019.5557

Appendix B – Used compound codes

Code/trivial name[a]	IUPAC name/SMILES notation/InChiKey[b]	Structural formula[b]
fenamiphos	(*RS*)-(ethyl 4-methylthio-*m*-tolyl isopropylphosphoramidate) O=P(OCC)(NC(C)C)OC1=CC=C(SC)C(C)=C1 ZCJPOPBZHLUFHF-UHFFFAOYSA-N	
Fenamiphos-sulfoxide (FOX, **M01**)	ethyl (3-methyl-4-(methylsulfinyl)phenyl) isopropylphosphoramidate CCOP(NC(C)C)(OC1=CC=C(C(C)=C1)S(C)=O)=O LUQMWGMGWJEGAT-UHFFFAOYSA-N	
Fenamiphos-sulfone (FON, **M02**)	ethyl (3-methyl-4-(methylsulfonyl)phenyl) isopropylphosphoramidate CCOP(NC(C)C)(OC1=CC=C(C(C)=C1)S(C)(=O)=O)=O LVNYJXIBJFXIRZ-UHFFFAOYSA-N	
Fenamiphos-sulfoxide-phenol (FOXP, **M12**)	3-methyl-4-(methylsulfinyl)phenol CC1=CC(O)=CC=C1S(C)=O YFQBELWMXKXATM-UHFFFAOYSA-N	
Fenamiphos-sulfone-phenol (FONP, **M13**)	3-methyl-4-(methylsulfonyl)phenol CC1=CC(O)=CC=C1S(=O)(C)=O KGPGKOSHODHUSR-UHFFFAOYSA-N	
Fenamiphos-sulfone-anisole (FANON, **M14**)	4-methoxy-2-methyl-1-(methylsulfonyl)benzene O=S(C1=CC=C(OC)C=C1C)(C)=O FCFWGOXRVWSOGG-UHFFFAOYSA-N	
Fenamiphos-phenol-sulfonic-acid (FPSA)	4-hydroxy-2-methylbenzenesulfonic acid O=S(C1=CC=C(O)C=C1C)(O)=O PYPXOMYXFFYJIF-UHFFFAOYSA-N	
Fenamiphos-phenol **(M11)**	3-methyl-4-(methylthio)phenol OC(C=C1C)=CC=C1SC VKALYYFVKBXHTF-UHFFFAOYSA-N	
des-isopropylamino fenamiphos sulfoxide or desamino fenamiphos sulfoxide **(M09)**	ethyl (3-methyl-4-(methylsulfinyl)phenyl) hydrogen phosphate O=P(OC1=CC=C(C(C)=C1)S(C)=O)(O)OCC CUKRJRGXLGRHSL-UHFFFAOYSA-N	

Code/trivial name[a]	IUPAC name/SMILES notation/InChiKey[b]	Structural formula[b]
des-isopropyl fenamiphos sulfoxide (M07)	ethyl (3-methyl-4-(methylsulfinyl)phenyl) phosphoramidate O=P(OCC)(N)OC1=CC=C(S(C)=O)C(C)=C1 GTSHDLNUJIPQOB-UHFFFAOYSA-N	

IUPAC: International Union of Pure and Applied Chemistry; SMILES: simplified molecular-input line-entry system; InChiKey: International Chemical Identifier Key.
(a): The metabolite name in bold is the name used in the conclusion.
(b): ChemBioDraw v.13.0.2.3021.