CONCLUSION ON PESTICIDE PEER REVIEW

EFSA Journal

APPROVED: 1 December 2021

doi: 10.2903/j.efsa.2022.7037

Peer review of the pesticide risk assessment for the active substance penthiopyrad in light of confirmatory data submitted

European Food Safety Authority (EFSA),
Jorge Borroto, Alba Brancato, Luis Carrasco Cabrera, Anna Federica Castoldi, Arianna Chiusolo, Angelo Colagiorgi, Mathilde Colas, Federica Crivellente, Chloe De Lentdecker, Mark Egsmose, Gabriella Fait, Varvara Gouliarmou, Franco Ferilli, Luna Greco, Frederique Istace, Samira Jarrah, Dimitra Kardassi, Roberto Lava, Renata Leuschner, Christopher Lythgo, Oriol Magrans, Iris Mangas, Ileana Miron, Tunde Molnar, Laura Padovani, Juan Manuel Parra Morte, Ragnor Pedersen, Hermine Reich, Miguel Santos, Rositsa Serafimova, Andrea Terron, Manuela Tiramani and Benedicte Vagenende

Abstract

The conclusions of EFSA following the peer review of the initial risk assessment carried out by the competent authority of the original rapporteur Member State United Kingdom supported by the new rapporteur Member State Sweden, for the pesticide active substance penthiopyrad are reported. The context of the peer review was that requested by the European Commission following the submission and evaluation of confirmatory information in the area of mammalian toxicology. The European Commission mandated EFSA to arrange a further peer review of the confirmatory data. The conclusions were reached on the basis of the evaluation of the representative uses of penthiopyrad as a fungicide on pome fruit, tomato, aubergines, cucurbits, cucumbers, courgettes and cereals. The reliable endpoints concluded as being appropriate for use in regulatory risk assessment, derived from the available studies and/or literature in the dossier peer reviewed, are presented. Concerns are identified.

Keywords: penthiopyrad, peer review, confirmatory data, risk assessment, pesticide, fungicide

Requestor: European Commission

Question number: EFSA-Q-2021-00047

Correspondence: pesticides.peerreview@efsa.europa.eu

Declarations of interest: The declarations of interest of all scientific experts active in EFSA's work are available at https://ess.efsa.europa.eu/doi/doiweb/doisearch.

Suggested citation: EFSA (European Food Safety Authority), Borroto J, Brancato A, Carrasco Cabrera L, Castoldi AF, Chiusolo A, Colagiorgi A, Colas M, Crivellente F, De Lentdecker C, Egsmose M, Fait G, Gouliarmou V, Ferilli F, Greco L, Istace F, Jarrah S, Kardassi D, Lava R, Leuschner R, Lythgo C, Magrans O, Mangas I, Miron I, Molnar T, Padovani L, Parra Morte JM, Pedersen R, Reich H, Santos M, Serafimova R, Terron A, Tiramani M and Vagenende B, 2022. Conclusion on the peer review of the pesticide risk assessment for the active substance penthiopyrad in light of confirmatory data submitted. EFSA Journal 2022;20(1):7037, 18 pp. https://doi.org/10.2903/j.efsa.2022.7037

ISSN: 1831-4732

The EFSA Journal is a publication of the European Food Safety Authority, a European agency funded by the European Union.

Summary

Penthiopyrad has been approved under Regulation (EC) No 1107/2009 on 1 May 2014 by Commission Implementing Regulation (EU) No 1187/2013. EFSA previously finalised a conclusion on this active substance on 11 April 2013 (EFSA, 2013).

It was a specific provision of the approval that the applicant was required to submit to the European Commission further data on

1) the non-relevance of metabolite M11 (3-methyl-1-{3-[(1-methyl-3-trifluoromethyl-1*H*-pyrazole-4-carbonyl)amino]thiophen-2-yl}pentanoic acid) for groundwater with the exception of evidence related to the risk of carcinogenicity, which is dependent on the classification of the parent and specified separately at (3) below;
2) the toxicological profile and the reference values of the metabolite PAM;
3) the relevance of the metabolites M11 (3-methyl-1-{3-[(1-methyl-3-trifluoromethyl-1*H*-pyrazole-4-carbonyl)amino]thiophen-2-yl}pentanoic acid), DM-PCA (3-trifluoromethyl-1*H*-pyrazole-4- carboxylic acid), PAM (1-methyl-3-trifluoromethyl-1*H*-pyrazole-4-carboxamide) and PCA (1-methyl-3-trifluoromethyl-1*H*-pyrazole-4-carboxylic acid) and their risk to contaminate groundwater, if penthiopyrad is classified under Regulation (EC) No 1272/2008 as carcinogenic cat. 2.

In accordance with the specific provision, the applicant, LKC UK Ltd on behalf of Mitsui Chemicals Agro Inc. and DuPont Crop Protection (now Corteva Agriscience), submitted relevant data in support of data requirements (1) and (2) above in September 2014, which were evaluated by the designated rapporteur Member State (RMS), United Kingdom, in the form of an addendum to the draft assessment report (United Kingdom, 2016). In compliance with guidance document SANCO 5634/2009-rev.6.1 (European Commission, 2013), the RMS distributed the addendum to Member States, the applicant and EFSA for comments on 1 April 2016. The RMS collated all comments in the format of a reporting table, which was submitted to EFSA on 24 June 2016. EFSA added its scientific views on the specific points raised during the commenting phase in column 4 of the reporting table and finalised the related Technical Report on 22 July 2016.

Point (3) of the confirmatory information has become obsolete since the Risk Assessment Committee of the European Chemicals Agency (ECHA) delivered an opinion on penthiopyrad in December 2015 concluding that penthiopyrad does not meet the criteria to be classified as carcinogenic in accordance with Regulation (EC) No 1272/2008.

In its Technical Report, EFSA indicated the need for expert discussion on the assessment of the toxicological profile of the metabolites M11 and PAM.

With a mandate of 19 January 2021, the European Commission asked EFSA to organise a further peer review of the evaluation by RMS of the confirmatory data submitted in relation to points (1) and (2) above, including expert discussion, where appropriate and to deliver its conclusions on the following points:

- The genotoxic potential of metabolite M11
- The toxicological profile of metabolite PAM

The metabolites M11 and PAM are considered relevant metabolites according to the European Commission guidance (European Commission, 2003) based on inconclusive genotoxicity and due to toxicological effects indicating potential for reproductive toxicity, respectively.

The metabolite PAM has a different toxicological profile than penthiopyrad. Lower toxicological reference values for PAM were set than for penthiopyrad and a separate consumer risk assessment was required for PAM. The plant and livestock residue definitions for risk assessment were finalised, while the finalisation of the residue definition for processed commodities is still pending data to address the behaviour of PAM under representative food processing conditions. A preliminary (not finalised) dietary consumer risk assessment, which did not consider possible PAM-derived residues in processed commodities, resulted in an estimate of short- and long-term PAM intakes that were below the derived toxicological reference values for PAM.

Considering the available FOCUS groundwater simulations for the representative uses assessed, the relevant groundwater metabolite M11 exceeded the parametric drinking water limit of 0.1 μg/L (80th percentile annual average recharge concentration moving below 1m) at just the FOCUS Hamburg scenario with a value of 0.129 μg/L from just the representative use for pome fruit. The metabolite PAM was exclusively found under photolytic conditions. Under these conditions the relevant

groundwater metabolite PAM was expected to exceed the parametric drinking water limit of 0.1 μg/L (80th percentile annual average recharge concentration moving below 1 m) at all of the FOCUS scenarios simulated for the uses assessed on pome fruit and spring cereals, and seven out of nine FOCUS scenarios for the winter cereal uses. For the uses on fruiting vegetables, the relevant groundwater metabolite PAM is expected to exceed 0.1 μg/L in one out of the five relevant FOCUS scenarios.

Though outside the scope of the confirmatory data assessment, it is noted that biological (fungicidal) activity screening data needed for the assessment of groundwater relevance for all the representative uses assessed, were not available for the groundwater metabolite DM-PCA.

Table of contents

Background

Penthiopyrad has been approved under Regulation (EC) No 1107/20091[1] on 1 May 2014 by Commission Implementing Regulation (EU) No 1187/2013[2]. EFSA previously finalised a conclusion on this active substance on 11 April 2013 (EFSA, 2013).

It was a specific provision of the approval that the applicant was required to submit to the European Commission further data on

1) the non-relevance of metabolite M11 for groundwater with the exception of evidence related to the risk of carcinogenicity, which is dependent on the classification of the parent and specified separately at 3);
2) the toxicological profile and the reference values of the metabolite PAM;
3) the relevance of the metabolites M11, DM-PCA, PAM and PCA and their risk to contaminate groundwater, if penthiopyrad is classified under Regulation (EC) No 1272/2008 as carcinogenic cat. 2.;

by 30 April 2016 for points (1) and (2) and the information set out in point (3) within six months from the notification of the classification decision concerning penthiopyrad.

In accordance with the specific provision, the applicant, LKC UK Ltd on behalf of Mitsui Chemicals Agro Inc. and DuPont Crop Protection (now Corteva Agriscience), submitted relevant data in support of data requirements (1) and (2) in September 2014, which was evaluated by the designated rapporteur Member State (RMS), United Kingdom, in the form of an addendum to the draft assessment report (United Kingdom, 2016). In compliance with guidance document SANCO 5634/2009-rev.6.1 (European Commission, 2013), the RMS distributed the addendum to Member States, the applicant and EFSA for comments on 1 April 2016. The RMS collated all comments in the format of a reporting table, which was submitted to EFSA on 24 June 2016. EFSA prepared a Technical Report (EFSA, 2016).

Point (3) of the confirmatory information has become obsolete since the Risk Assessment Committee of the European Chemicals Agency (ECHA) delivered an opinion[3] on penthiopyrad in December 2015 concluding that penthiopyrad does not meet the criteria to be classified as carcinogenic in accordance with Regulation (EC) No 1272/2008.

In its Technical Report, EFSA indicated the need for expert discussion on the assessment of the toxicological profile of the metabolites M11 and PAM.

With a mandate of 19 January 2021, the European Commission asked EFSA to organise a further peer review of the evaluation by RMS of the confirmatory data submitted in relation to points (1) and (2) above, including expert discussion, where appropriate and to deliver its conclusions. In particular, the following points were discussed in the mandate:

- The genotoxic potential of metabolite M11.

It is noted that M11 is not predicted to occur in groundwater above the parametric legal level of 0.1 μg/L in the geoclimatic situations represented by all nine FOCUS scenarios for the representative uses assessed; however, further discussion is considered useful to ensure harmonised assessments in case of other uses that may be authorised by Member States and in view of the forthcoming renewal assessment of penthiopyrad.

Diverging views on the results of the in vitro studies and the overall conclusion on whether sufficient information is available to conclude on the genotoxic potential of M11 should be further considered.

- The toxicological profile of metabolite PAM.
  - 'Diverging views regarding the interpretation of the results of the subacute toxicity studies conducted with PAM regarding its potential for reproductive toxicity should be considered.
  - If the reference values are amended, the consumer risk assessment from exposure to PAM should be updated.

[1] Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21 October 2009 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.

[2] Commission Implementing Regulation (EU) No 1187/2013 of 21 November 2013 approving the active substance penthiopyrad, 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, and amending the Annex to Commission Implementing Regulation (EU) No 540/2011. OJ L 313, 22.11.2013, p.42–46.

[3] Opinion proposing harmonised classification and labelling at EU level of Penthiopyrad (ISO); (*RS*)-*N*-[2-(1,3-dimethylbutyl)-3-thienyl]-1-methyl-3-(trifluoromethyl)pyrazole-4-carboxamide CLH-O-0000001412-86-78/F. Adopted 4 December 2015.

- The need for further toxicological data to address the toxicological relevance of PAM as a groundwater metabolite should also be considered, in view of the forthcoming renewal assessment of penthiopyrad'.

EFSA was requested to deliver its conclusions on the above points by 30 November 2021.

The addendum of the original RMS United Kingdom (United Kingdom, 2016) and the reporting table included in the Technical Report (EFSA, 2016) were discussed at the Pesticides Peer Review Experts' teleconference on mammalian toxicology in June 2021. The EFSA Scientific Committee Cross-cutting Working Group (WG) on Genotoxicity (from now on 'WG genotoxicity') was requested to provide advice on the genotoxic potential of metabolite M11 in April 2021. The advice was taken into account by the experts at the Pesticides Peer Review Experts' teleconference on mammalian toxicology. Details of the issues discussed, together with the outcome of these discussions were included in the meeting report.

A final consultation on the conclusions arising from the peer review took place with Member States via a written procedure in October–November 2021.

The conclusions laid down in this report were reached on the basis of the peer review of the RMS's evaluation of the confirmatory data submitted in relation to mammalian toxicology supported by the new RMS Sweden. A key supporting document to this conclusion is the peer review report, which is a compilation of the documentation developed to evaluate and address all issues raised in the peer review, from the compilation of comments in the reporting table to the conclusion. The peer review report (EFSA, 2021b) comprises the following documents, in which all views expressed during the course of the peer review, including minority views, can be found:

- the report of the scientific consultation with Member State experts including the minutes of the WG genotoxicity;
- the comment received on the draft EFSA conclusion.

Given the importance of the DAR including its final addendum (United Kingdom, 2016) and the peer review report, these documents are considered as background documents to this conclusion.

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

The active substance and the formulated product

Penthiopyrad is the ISO common name for (*RS*)-*N*-[2-(1,3-dimethylbutyl)-3-thienyl]-1-methyl-3-(trifluoromethyl)pyrazole-4-carboxamide (IUPAC).

The representative formulated products for the evaluation were '20 EC', an emulsifiable concentrate (EC) containing 200 g/L pure penthiopyrad and '20 SC', a suspension concentrate (SC) containing 200 g/L pure penthiopyrad.

The representative uses evaluated comprise (i) spraying for control of a range of pathogenic fungi in the field and greenhouses on tomatoes, aubergines, cucurbits, cucumbers and courgettes and in the field on pome fruit for '20 SC' and (ii) foliar and ear diseases control on cereals for '20 EC'.

Conclusions of the evaluation

The applicant has submitted to the European Commission by the deadline of 30 April 2016 studies to provide further information to assess:

1) the non-relevance of metabolite M11 (3-methyl-1-{3-[(1-methyl-3-trifluoromethyl-1*H*-pyrazole-4-carbonyl)amino]thiophen-2-yl}pentanoic acid) for groundwater with the exception of evidence related to the risk of carcinogenicity, which is dependent on the classification of the parent and specified separately at (3) below;
2) the toxicological profile and the reference values of the metabolite PAM;
3) the relevance of the metabolites M11, DM-PCA, PAM and PCA and their risk to contaminate groundwater, if penthiopyrad is classified under Regulation (EC) No 1272/2008 as carcinogenic cat. 2.

Point (3) of the confirmatory information has become obsolete since the Risk Assessment Committee of the European Chemicals Agency (ECHA) delivered an opinion[3] on penthiopyrad in December 2015 concluding that penthiopyrad does not meet the criteria to be classified as carcinogenic in accordance with Regulation (EC) No 1272/2008.

The assessment of the information was presented in revised confirmatory data addenda in April 2016, updated in June 2016 (United Kingdom, 2016).

1. Mammalian toxicology

The toxicological profile of metabolites M11 and PAM was discussed during the Pesticide Peer Review Experts' teleconference TC 55 (June 2021) following a consultation with the WG genotoxicity on the genotoxic potential of M11 (April 2021).

Further discussion on the toxicological profile of DM-PCA and PCA did not take place under this peer review of confirmatory data. Under the previous peer review, EFSA concluded that the reference values of penthiopyrad can apply to metabolites DM-PCA and PCA (EFSA, 2013).

Regarding the metabolite **M11**, the experts agreed with the advice given by the WG genotoxicity. The WG genotoxicity considered the *in vitro* gene mutation assay (mouse lymphoma assay, MLA) as inconclusive because of limitations of the study, i.e. incomplete analysis with respect to small and large colonies at lower concentrations, precipitation observed in several concentrations and selection of higher concentrations than the currently recommended in the OECD test guideline. Given the limitations of the available *in vitro* gene mutation assay, further data, i.e. a new MLA would be needed to clarify the *in vitro* mutagenic potential of M11. Given that the relevance assessment is triggered for M11 (see Section 3), following the European Commission guidance (European Commission, 2003) M11 is considered relevant based on inconclusive genotoxicity.

Regarding the metabolite **PAM**, all the experts agreed that, following the European Commission guidance (European Commission, 2003), PAM should be considered a relevant groundwater metabolite based on the toxicological effects observed in bone tissues and male reproductive organs, indicating potential for reproductive toxicity. As for the risk assessment, the experts agreed that the metabolite PAM is showing a different toxicological profile compared to the parent compound and specific reference values should apply. All the experts agreed with the proposal of the RMS for an acceptable daily intake (ADI) of 0.0024 mg/kg body weight (bw) per day and an acute reference dose (ARfD) of 0.024 mg/kg bw based on the no observed adverse effect level (NOAEL) of 7.3 mg/kg bw per day for toxicological effects on the liver (bile duct), bones, bone joint and thymus, applying an uncertainty factor of 3,000 and 300 to account for the respective limited databases.

2. Residues

Based on consideration of the toxicological profile and the occurrence of metabolites in the different plant commodities in metabolism studies and field trials, it was agreed during the peer review (EFSA, 2013) to provisionally set the plant **residue definition** for consumer risk assessment as follows: (1) Sum of penthiopyrad and metabolite 753-A-OH, expressed as penthiopyrad, and (2) PAM.

There was indication that PAM has a different toxicological profile than penthiopyrad. However, further data were necessary at that time to conclude on the toxicological profile of PAM, and consequently to finalise the residue definition for dietary risk assessment.

The toxicological assessment of further information for metabolite PAM led to the conclusion that PAM has a different toxicological profile than penthiopyrad and therefore, specific reference values apply for PAM (see Section 1). Hence, a separate consumer risk assessment for PAM is necessary.

The plant **residue definition** for risk assessment can therefore be finalised and set as (1) Sum of penthiopyrad and metabolite 753-A-OH, expressed as penthiopyrad, and (2) PAM. With regard to plant processed commodities, a residue definition cannot be finalised as the data gap identified by the peer review (EFSA, 2013) for investigation of the behaviour of PAM under conditions simulating industrial and household processing is still pending, and the necessity of this study for a consumer risk assessment has been confirmed by the recent Art. 12 MRL review (EFSA, 2021a).

The livestock residue definition for risk assessment is also confirmed as (1) Penthiopyrad and (2) PAM, separately.

As for the lower TRV's set for PAM and the observed residue situation for PAM in the available field trials in wheat, a data gap is set for two additional residue trials to support the representative use in wheat, rye and triticale in SEU (see Section 7). Previously, completion of the SEU data set has been waived based on more critical penthiopyrad levels in the samples from NEU trials. Following this targeted review on PAM, the waiver is no longer applicable as the residue levels of PAM appear to be more critical in the wheat commodities in SEU residue trials. The data gap identified in EFSA's previous conclusion (EFSA, 2013) for two additional residue trials in barley in SEU is still applicable. However,

the submission of two additional SEU residue trials each in wheat and barley is not expected to result in a significant change in the consumer risk assessment.

The **dietary consumer risk assessment** conducted with the EFSA PRIMo rev.3.1 for residues of PAM in raw agricultural commodities and in terms of the representative uses indicates that the highest dietary chronic exposure is 10% of the ADI of 0.0024 mg/kg bw per day for PAM, and that the highest dietary acute exposure is 6% of the ARfD of 0.024 mg/kg bw for PAM. The consumer risk assessment is preliminary as it did not consider potential PAM-derived residues in processed commodities because their identity and relevance are unknown (data gap leading to an assessment not finalised). The issue is specifically relevant for the uses in pome fruit, barley and oats where PAM residue levels in the raw commodities trigger the investigation of the residue behaviour during food processing.

Additional consumer exposure to residues of metabolites PAM in groundwater abstracted for drinking water supply was expected based on the PEC calculations (see Section 3), however, a specific consumer risk assessment was not conducted as following the European Commission guidance (European Commission, 2003), PAM is considered a relevant groundwater metabolite for its toxicological properties (see Sections 1 and 4).

3. Environmental fate and behaviour

The outcome of the peer review (EFSA, 2013) in the environmental fate and behaviour relevant to the pertinent soil metabolites that influence the outcome of the groundwater modelling of all the metabolites is included here for completeness. Additional confirmatory data substance properties for metabolite M11 have been integrated into this assessment.

The route and rate of degradation of penthiopyrad under dark aerobic conditions were investigated in six soils with ^{14}C-pyrazole or ^{14}C-thienyl radio labelled compound. All the soils were considered representative of EU agricultural soils (including a non-volcanic Japanese soil). Penthiopyrad exhibits medium to very high persistence in soil in these experiments. Metabolite DM-PCA was observed at levels above 10% AR. The levels of metabolites 753-A-OH, 753-T-DO, M11 and M12 are either above 5% in two consecutive data points or are still increasing at the end of the study with potential to exceed the 5% AR and need to be considered with respect to potential groundwater contamination. Metabolite M9 (unidentified), which is also increasing at the end of some experiments, is considered not to have the potential to reach the 5% AR level on the basis of the levels of remaining parent in those experiments. From the kinetic analysis of the experiments performed with the parent supplemented with some experiments where metabolite DM-PCA is directly applied to soil, it may be concluded that 753-A-OH and 753-T-DO exhibit moderate persistence (however limitation on the reliability in the half-lives calculated and the data gap identified, see below) and DM-PCA moderate to high persistence in soil (FOCUS, 2006). No kinetic data are available for metabolite M12. During the previous peer review it had been agreed that for M12, a structurally closely related isomer of metabolite 753-A-OH, no specific exposure assessment would be needed since the one performed for 753-A-OH could be applied to M12. For M11 a metabolite dosed dark aerobic incubation was available in 4 soils where it exhibited low to moderate persistence. Unextracted residues after 90 days amounted to 22.0–26.1% AR. Mineralisation (as CO_2) was 6–10.4% AR after 90 days.

Possible enantioselective degradation of penthiopyrad was investigated in 4 of the 6 laboratory degradation experiments. Enantioselective degradation was observed in all soils investigated. The applicant claimed that enantioselectivity was only apparent due to inaccuracies in the applied analytical method and considered the issue not relevant on the basis of presumed similar fungicidal activity of both isomers.

The appropriateness of the extraction procedure used in the laboratory degradation studies has been assessed during the previous peer review. It was noted that in this case the reasoning behind the selection of the extraction method had not been provided by the applicant and the number of extraction steps is limited in relation to common practice. The jump from mild extraction steps (acetonitrile: water [4:1] and acetonitrile/0.1 N NH_4CO_3) to harsh extraction (without intermediate extractions steps) may explain the high amount (up to 8%) of unmodified parent found in the harsh extraction step. The amount extracted in the harsh step was not considered in the calculation of the laboratory DT_{50}. However, the experts agreed that further data in relation to the degradation of the parent in laboratory studies are not needed since field studies are available and no impact on the exposure assessment is expected.

In a number of experiments performed with penthiopyrad there is practically no decline of the metabolites 753-A-OH and 753-T-DO. Therefore, high uncertainty is associated with the half-lives

calculated. The use of a long default half-life as a worst case for the assessment was not considered appropriate during the peer review, since these metabolites are not terminal metabolites. Therefore, a data gap for dark aerobic studies to directly investigate the degradation of metabolites 753-A-OH and 753-T-DO in soil was identified (see Section 7).

A study to investigate the degradation of penthiopyrad in soil under anaerobic conditions was performed on American soil. Once the anaerobic conditions were reached, the degradation slowed down significantly (penthiopyrad $DT_{50\ anaerobic} > 1$ year). Under these conditions, the only metabolite exceeding 5% AR was DM-PCA. Photolysis in soil was investigated in an experiment under simulated sunlight for 15 days of continuous irradiation (corresponding to midsummer 29 days at 50°N). Penthiopyrad showed rapid and extensive photolysis producing up to 16 different metabolites. Metabolites PAM and PCA reached maximum levels of 47% AR (on day 10) and 36% AR (on day 7) respectively. The rest of the metabolites identified accounted for less than 3% AR during the study.

The dissipation of penthiopyrad under bare soil field conditions was investigated in six locations in North America and four locations in Europe. Additionally, field dissipation was investigated under cropped conditions in two of the USA sites. Only European sites were analysed following FOCUS kinetics and were used in the exposure assessment presented in the EU dossier. During the previous peer review, it was agreed that, in line with previous assessments, all available relevant information should be used to derive the EU end points. Furthermore, in this case, kinetic parameters derived from one of the four EU field dissipation studies have been assessed as unreliable. Therefore, during the peer review, a data gap was identified (see Section 7) to assess the applicability of the North American field dissipation studies (including influence of photolytic processes). A data gap for an additional field dissipation study in the EU would be identified in case none of the North American field dissipation studies is found relevant to the EU conditions. The striking feature of all field studies available is the significant contribution of photolysis that results in very fast degradation of penthiopyrad (DT_{50} = 0.8–8.9 days) and the formation of two new major soil metabolites not detected in the dark aerobic studies but found in the photolysis in soil study. From the two North American experiments performed on cropped fields, it is apparent that photolysis also may play a significant role in the dissipation of penthiopyrad under cropped conditions. In total, three major metabolites were observed in the field studies: PAM, PCA and DM-PCA (> 10% AR in at least one field site). Due to the high uncertainty associated with the input parameters derived from the multi-compartmental kinetic analysis of photolysis metabolites, it was agreed that only DT_{50} of metabolites derived directly by fitting data from the maxima observed could be used to perform the exposure assessment based on the photolysis route.

Extraction methods employed in the field studies were even milder than the ones used in laboratory studies (e.g. step with acetonitrile/0.1 N NH_4CO_3 was not performed). During the previous peer review, a data gap was identified (see Section 7) for the applicant to justify the appropriateness of the soil extraction method used in the field studies for the parent and the metabolites.

As a result of the two remarkably different routes of degradation observed in the dark laboratory studies and the illuminated field dissipation studies, assessment needs to be performed to address two alternative realistic worst cases where contribution of light is high or low. The actual situation for the representative uses can be expected to lie in between the two cases considered.

The mobility of penthiopyrad and its metabolites DM-PCA, PCA, PAM, 753-A-OH, 753-T-DO and M11 was assessed by batch adsorption/desorption studies in up to five soils for the parent and four soils for the metabolites. According to the results of these studies, penthiopyrad may be considered of low mobility, metabolites DM-PCA, PCA, PAM, M11 as very highly mobile, 753-A-OH as highly mobile and 753-T-DO as of medium mobility. For the metabolites DM-PCA and 753-A-OH some pH dependence was observed. The experts in the Pesticides Peer Review teleconference 78 agreed that it was not necessary to consider pH dependence of these metabolites in the groundwater modelling and mean adsorption parameters were used for the EU exposure assessment.

Penthiopyrad was stable to hydrolysis in buffer aqueous solutions (25°C, pH 4, 5, 7 and 9; from measurements performed at 50°C).

The potential for groundwater contamination was assessed by calculation of the 20 years 80th percentile concentration at 1 m depth for penthiopyrad and its metabolites M11, DM-PCA, PCA, PAM, 753-A-OH and 753-T-DO with the FOCUS GW II scheme (FOCUS, 2000,2009; EFSA, 2008).[4] Leaching resulting from the representative uses was simulated by the RMS using the peer review agreed input

[4] A Q10 of 2.58 (EFSA, 2008) and Walker equation coefficient of 0.7 was used in these simulations and for the normalisation of the degradation input parameters used in the modelling.

parameters for either dark pathway (using laboratory degradation rate) or the photolytic pathway (using field degradation rates) with FOCUS models PEARL 4.4.4 and PELMO 4.4.2 and for M11 PELMO 5.5.3 for the available scenarios following the representative Good Agricultural Practice (GAP) for pome fruit, tomatoes/cucurbits (edible peel), spring and winter cereals. No specific assessment has been presented for greenhouse uses. Therefore equivalent field use results are considered to represent worst case assessment of the greenhouse ones. Results for groundwater modelling except for M11 and penthiopyrad were as reported in EFSA (2013) and have been included in Appendix A. According to these calculations, M11 did not exceed the parametric drinking water limit of 0.1 μg/L for any of the uses and scenarios simulated with the exception that for the representative GAP for pome fruit at just the Hamburg scenario a value of 0.129 μg/L was predicted (only the dark pathway is relevant for M11). Metabolite PAM was exclusively found under photolytic conditions. Under these conditions metabolite PAM was expected to exceed the limit of 0.1 μg/L in the majority or all of the scenarios simulated for pome fruit, spring cereals and winter cereal uses. For the use on tomatoes/cucurbits (edible peel), metabolite PAM is expected to exceed 0.1 μg/L in one of the five relevant scenarios. Both these metabolites have been assessed as relevant groundwater metabolites (see Sections 1 and 4).

4. Overview of the risk assessment of compounds that are the subject of the mandate for the compartment groundwater

Table 1: Groundwater[(a)]

Compound (name and/or code)	**> 0.1 μg/L at 1 m depth for the representative uses[(b)] Step 2**	**Biological (pesticidal) activity/ relevance Step 3a**	**Hazard identified Steps 3b. and 3c**	**Consumer RA triggered Steps 4 and 5**	**Human health relevance**
M11 (dark laboratory experiments)	Yes but only at the Hamburg scenario of pome fruit 0.129 μg/L. No for other uses and scenarios	No	Yes **Relevant** based on inconclusive genotoxicity potential.	Not required due to inconclusive genotoxicity potential concluded at Step 3c.	Yes
PAM (photolysis metabolite observed in field studies)	Yes > 0.75 μg/L in 2/9 scenarios of pome fruit, 1/ 6 scenarios of spring cereals. > 0.1 μg/L in 9/9 scenarios of pome fruit, 1/5 scenarios of fruiting vegetables, 6/6 scenarios of spring cereals and 7/9 scenarios of winter cereals	No data	Yes **Relevant** based on the hazard for reproductive toxicity.	Not required due to the hazard for reproductive toxicity concluded at Step 3c.	Yes

(a): Assessment according to European Commission guidance of the relevance of groundwater metabolites (2003).
(b): FOCUS scenarios or relevant a lysimeter.

5. Concerns and related data gaps for the representative uses evaluated

5.1. 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 one or more of the representative uses in line with the uniform principles in accordance with Article 29(6) of Regulation (EC) No 1107/2009 and as set out in Commission Regulation (EU) No 546/2011[5] and if the issue is of such importance that it could, when finalised, become a concern (which would also be listed as a critical area of concern if it is of relevance to all representative uses).

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.

The following issues or assessments that could not be finalised have been identified, together with the reasons including the associated data gaps where relevant, which are reported directly under the specific issue to which they are related. Issues or assessments that could not be finalised in the previous EFSA conclusion (EFSA, 2013) which were not affected by the confirmatory data assessment (e.g. 'The risk to soil macroorganisms could not be finalised with the available data' from EFSA, 2013) still remain valid.

1) The residue definition for processed commodities and a dietary consumer risk assessment that adequately addresses the residues in processed commodities could not be finalised.
    a) Data to address the behaviour of PAM under conditions simulating industrial and household processing were not available and are still required (relevant for the uses in pome fruit and barley/oats; see Section 2).
2) Regarding groundwater exposure and the scope of the confirmatory data assessment being metabolites M11 and PAM, all the necessary assessments have been finalised. However as indicated in Table 2, the groundwater relevance assessment for metabolite DM-PCA could not be finalised, for all the representative uses assessed, while data on its biological (fungicidal) activity was not available, consequently a final conclusion on groundwater relevance for DM-PCA was not available.
    a) Biological (fungicidal) activity screening data needed for the assessment of groundwater relevance were not available for groundwater metabolite DM-PCA (relevant for all representative uses evaluated; see Section 6 of EFSA (2013) regarding DM-PCA).

5.2. 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.

The following critical areas of concern are identified, together with any associated data gaps, where relevant, which are reported directly under the specific critical area of concern to which they are related:

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

No critical areas of concern were identified in this peer review.

The critical area of concern identified in EFSA (2013) is no longer relevant.

6. Overview of the concerns identified for each representative use considered (Table 2)

Table 2: Overview of concerns reflecting the issues not finalised, critical areas of concerns and the risks identified that may be applicable for some but not for all uses or risk assessment scenarios

Representative use		Pome fruit	Tomato & aubergine greenhouse except France	Tomato & aubergine greenhouse France	Tomato & aubergine field direct consumption
		Foliar spray	Foliar spray	Foliar spray	Foliar spray
Consumer risk	Risk identified				
	Assessment not finalised	X[1]			
Groundwater exposure to active substance	Legal parametric value breached				
	Assessment not finalised				
Groundwater exposure to metabolites	Legal parametric value breached	X all FOCUS scenarios	1/5 FOCUS scenarios	1/5 FOCUS scenarios	1/5 FOCUS scenarios
	Parametric value of 10 µg/L[(a)] breached	8/9 FOCUS scenarios[(b)]			
	Assessment not finalised	X[(b)]	X[(b)]	X[(b)]	X[(b)]

Representative use		Tomato & aubergine field industrial processing	Tomato & aubergine field France	Cucurbits (edible peel) greenhouse	Cucurbits (edible peel) field
		Foliar spray	Foliar spray	Foliar spray	Foliar spray
Consumer risk	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	1/5 FOCUS scenarios	1/5 FOCUS scenarios	1/5 FOCUS scenarios	1/5 FOCUS scenarios
	Parametric value of 10 µg/L[(a)] breached				
	Assessment not finalised	X[(b)]	X[(b)]	X[(b)]	X[(b)]

Representative use		Wheat rye triticale	Barley oats		
		Foliar spray	Foliar spray		
Consumer risk	Risk identified				
	Assessment not finalised		X[1]		
Groundwater exposure to active substance	Legal parametric value breached				
	Assessment not finalised				
Groundwater exposure to metabolites	Legal parametric value breached	13/15 FOCUS scenarios	13/15 FOCUS scenarios		
	Parametric value of 10 µg/L[(a)] breached	14/15 scenarios[(b)]	14/15 scenarios[(b)]		
	Assessment not finalised	X[(b)]	X[(b)]		

(a): Value for non-relevant metabolites prescribed in SANCO/221/2000-rev. 10 final, European Commission (2003).
(b): Relates to metabolite DM-PCA, see levels in Appendix A, expected to be non-relevant regarding human health considering the consumer risk assessment available in Section 3 of EFSA (2013), but data on biological (fungicidal) activity was not available, (see Section 5.1, point 2), so a final conclusion on groundwater relevance for this metabolite is outstanding.

7. List of other outstanding issues

Remaining data gaps do not lead to critical areas of concern or issues not finalised but considered necessary to comply with the data requirements, and which are relevant for some or all of the representative uses assessed at EU level and are related to the consumer exposure assessment or groundwater exposure or groundwater metabolite relevance assessment. Although not critical, these data gaps may lead to uncertainties in the assessment and are considered relevant.

These data gaps are identified in the focussed peer review process of confirmatory data and refer only to representative uses assessed. Data gaps identified in the previously finalised EFSA conclusion on the active substance (EFSA, 2013) that were not associated with the topics of the focussed peer review process of confirmatory data remain unchanged.

The data gaps mentioned above are listed in the order of the sections

1) Two additional residues trials in cereals in S EU to complete the minimum number of trials required for a major crop (relevant for the representative use in cereals: wheat, rye, triticale; see Section 2).
2) To investigate degradation of metabolites 753-A-OH and 753-T-DO in soil under dark aerobic conditions with studies where the metabolites are applied directly to soil (relevant for all representative uses evaluated; see Section 3).
3) To justify the appropriateness of the soil extraction method used in the field dissipation studies for the parent and the metabolites (relevant for all representative uses evaluated; see Section 3).
4) To assess the applicability of the North American field dissipation studies to the assessment of the fate and behaviour of penthiopyrad in the EU (including influence of photolytic processes). A data gap for an additional field dissipation study in EU would be identified in case none of the North American field dissipation studies is found relevant to the EU conditions (relevant for all representative uses evaluated; see Section 3).
5) Biological (fungicidal) activity screening data needed for the assessment of groundwater relevance were not available for groundwater metabolites PAM and PCA (relevant for all representative uses evaluated; see section 4 regarding PAM and section 6 of EFSA (2013) regarding PCA).

References

EFSA (European Food Safety Authority), 2008. Opinion on a request from EFSA related to the default Q10 value used to describe the temperature effect on transformation rates of pesticides in soil. EFSA Journal 2008;6 (1):622, 32pp. https://doi.org/10.2903/j.efsa.2008.622

EFSA (European Food Safety Authority), 2013. Conclusion on the peer review of the pesticide risk assessment of the active substance penthiopyrad. EFSA Journal 2013;11(2):3111, 144 pp. https://doi.org/10.2903/j.efsa.2013.3111

EFSA (European Food Safety Authority), 2016. Technical report on the outcome of the consultation with Member States, the applicant and EFSA on the pesticide risk assessment for penthiopyrad in light of confirmatory data. EFSA Supporting Publication 2016;EN-1072, 21 pp. https://doi.org/10.2903/j.efsa.2016.1072

EFSA (European Food Safety Authority), Bellisai G, Bernasconi G, Brancato A, Carrasco Cabrera L, Ferreira L, Giner G, Greco L, Jarrah S, Kazocina A, Leuschner R, Magrans JO, Miron I, Nave S, Pedersen R, Reich H, Ruocco S, Santos M, Scarlato AP, Theobald A, Vagenende B and Verani A, 2021a. Reasoned Opinon on the review of the existing maximum residue levels for penthiopyrad according to Article 12 of Regulation (EC) No 396/2005. EFSA Journal 2021;19(9):6810, 112 pp. https://doi.org/10.2903/j.efsa.2021.6810

EFSA (European Food Safety Authority), 2021b. Peer review report to the conclusion regarding the peer review of the pesticide risk assessment of the active substance penthiopyrad in light of confirmatory data. Available online: www.efsa.europa.eu

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, 2013. Guidance document on the procedures for submission and assessment of confirmatory information following approval of an active substance in accordance with Regulation (EC) No 1107/2009. SANCO 5634/2009-rev. 6.1.

FOCUS (Forum for the Co-ordination of Pesticide Fate Models and their Use), 2000. "FOCUS Groundwater Scenarios in the EU review of active substances". Report of the FOCUS Groundwater Scenarios Workgroup, EC Document Reference SANCO/321/2000- rev.2. 202 pp, as updated by the Generic Guidance for FOCUS groundwater scenarios, version 1.1 dated April 2002.

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 Work Group on Degradation Kinetics, EC Document Reference Sanco/ 10058/2005 Version, 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 ground water 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.

United Kingdom, 2016. Addendum to the assessment report on penthiopyrad, confirmatory data, April 2016, revised in June 2016. Available online: www.efsa.europa.eu

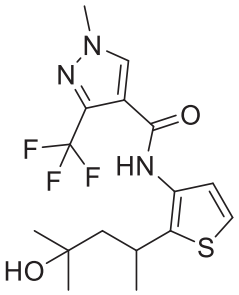
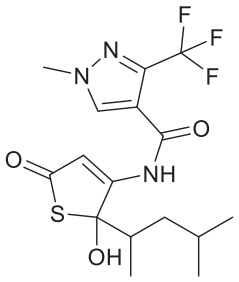
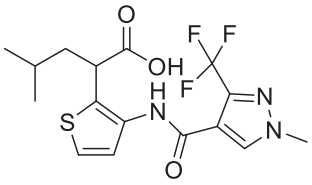
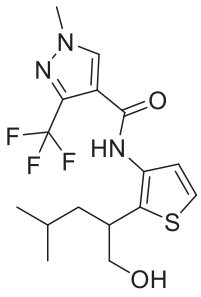
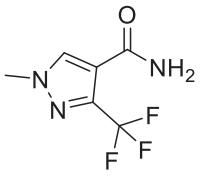
Abbreviations

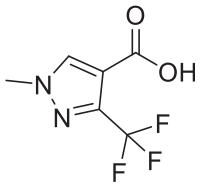
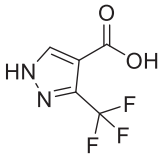
ADI	acceptable daily intake
AR	applied radioactivity
ARfD	acute reference dose
bw	body weight
DAR	draft assessment report
ECHA	European Chemicals Agency
EEC	European Economic Community
FOCUS	Forum for the Co-ordination of Pesticide Fate Models and their Use
GAP	Good Agricultural Practice
ISO	International Organization for Standardization
IUPAC	International Union of Pure and Applied Chemistry
InChiKey	International Chemical Identifier Key
MRL	maximum residue level
OECD	Organisation for Economic Co-operation and Development
SC	suspension concentrate
SMILES	simplified molecular-input line-entry system

Appendix A – List of end points for the active substance and the representative formulation relevant for the confirmatory data assessed

Appendix A can be found in the online version of this output ('Supporting information' section): https://doi.org/10.2903/j.efsa.2022.7037

Appendix B – Used compound codes

Code/trivial name[a]	IUPAC name/SMILES notation/InChiKey[b]	Structural formula[c]
753-A-OH	*N*-(2-(4-hydroxy-4-methylpentan-2-yl)thiophen-3-yl)-1-methyl-3-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide O = C(C1=CN(C)N=C1C(F)(F)F)NC2=C(C(CC(C)(O)C)C)SC=C2 PTOONGKKGPZDRB-UHFFFAOYSA-N	
753-T-DO	*N*-(2-hydroxy-2-(4-methylpentan-2-yl)-5-oxo-2,5-dihydrothiophen-3-yl)-1-methyl-3-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide O = C(C1=CN(C)N=C1C(F)(F)F)NC(C(C(CC(C)C)C)(O)S2)=CC2=O XHRDZJHMDZCQRN-UHFFFAOYSA-N	
M11	4-methyl-2-(3-(1-methyl-3-(trifluoromethyl)-1*H*-pyrazole-4-carboxamido)thiophen-2-yl)pentanoic acid CC(C)CC(C1=C(NC(C2=CN(C)N=C2C(F)(F)F)=O)C=CS1)C(O)=O LVRRGIXLLWBUEI-UHFFFAOYSA-N	
M12	*N*-(2-(1-hydroxy-4-methylpentan-2-yl)thiophen-3-yl)-1-methyl-3-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide O = C(NC1=C(SC=C1)C(CO)CC(C)C)C2=CN(N=C2C(F)(F)F)C WSMRCHGAQBXTGN-UHFFFAOYSA-N	
PAM	1-methyl-3-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide O = C(C1=CN(C)N=C1C(F)(F)F)N UTBJLKDVQNCKAS-UHFFFAOYSA-N	

Code/trivial name[a]	IUPAC name/SMILES notation/InChiKey[b]	Structural formula[c]
PCA	1-methyl-3-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid O = C(C1=CN(C)N=C1C(F)(F)F)O FZNKJQNEJGXCJH-UHFFFAOYSA-N	
DM-PCA	3-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid O = C(C1=CNN=C1C(F)(F)F)O VHKMTORCXXPIFI-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 Ultra v.13.0.2.3021.
(c): ChemBioDraw Ultra v.13.0.2.3021.