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## Updated peer review of the pesticide risk assessment of the active substance mepanipyrim

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### Abstract

The conclusions of the EFSA following the peer review of the initial risk assessments carried out by the competent authorities of the rapporteur Member State, Belgium, and co-rapporteur Member State, Greece, for the pesticide active substance mepanipyrim 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 mepanipyrim as a fungicide on table and wine grapes and in field and protected strawberries and tomatoes. The conclusions were updated with regard to the endocrine-disrupting properties following a mandate received from the European Commission in January 2019. 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 reported where identified.

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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. Meplanipyrim 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), Belgium, and co-rapporteur Member State (co-RMS), Greece, received an application from K-I Chemical Europe SA/NV for the renewal of approval of the active substance meplanipyrim. Complying with Article 8 of the Regulation, the RMS checked the completeness of the dossier and informed the applicant, the co-RMS, the European Commission and the European Food Safety Authority (EFSA) about the admissibility.

The RMS provided its initial evaluation of the dossier on meplanipyrim in the renewal assessment report (RAR), which was received by EFSA on 3 May 2016. In accordance with Article 12 of the Regulation, EFSA distributed the RAR to the Member States and the applicant, K-I Chemical Europe SA/NV, for comments on 12 July 2016. EFSA also provided comments. In addition, EFSA conducted a public consultation on the RAR. EFSA collated and forwarded all comments received to the European Commission on 13 September 2016.

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, residues and ecotoxicology.

In accordance with Article 13(1) of the Regulation, EFSA should adopt a conclusion on whether meplanipyrim 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 meplanipyrim as a fungicide on table and wine grapes, field and protected strawberries and tomatoes, as proposed by the applicant. EFSA published its conclusion on the peer review of the pesticide risk assessment of meplanipyrim on 12 May 2017 (EFSA Journal 2017;15(6):4852). Subsequently, the conclusions were updated with regard to the endocrine-disrupting properties following a mandate received from the European Commission in January 2019.

Full details of the representative uses can be found in Appendix A of this report.

The use of meplanipyrim according to the representative uses proposed at EU level (Southern zone) results in a sufficient fungicidal efficacy against grey mould.

In the section **identity, physical chemical properties and analytical methods**, a data gap was identified for a method of monitoring for residues in body fluids and tissues.

In the **mammalian toxicology** area, data gaps were identified in relation to the absence of comparative interspecies metabolism study *in vitro*, the need for quantitative structure–activity relationship (QSAR) data and repeated dose toxicity data relevant to consumer exposure for the metabolite M31, and to address the toxicological relevance of two impurities present in the technical specification. Since meplanipyrim was found to be phototoxic *in vitro*, and there is currently no validated test *in vivo*, the phototoxic potential of the substance could not be finalised. Operator and worker exposure were found to exceed the acceptable operator exposure level (AOEL) in some scenarios even when using personal protective equipment.

In the **residue** section, in addition to the request in the mammalian toxicology area to address the toxicological profile of metabolite M31, a data gap was identified for the investigation of the fate of M31 under standard processing conditions. Hence, the consumer risk assessment could not be finalised considering the outstanding data to finalise the residue definitions in primary crops and in processed commodities. Moreover, an additional indoor good agricultural practice (GAP) compliant residue trial on tomatoes is required and a data gap for the determination of meplanipyrim and M31 residues in pollen and bee products for human consumption resulting from residues taken up by honeybees at blossom from grapes, field grown strawberries and field grown tomatoes was not addressed (data gap).

The data available on **environmental fate and behaviour** are sufficient to carry out the required environmental exposure assessments at the EU level for the representative uses. A data gap was identified for information on the effect of water treatment processes on the nature of residues potentially present in surface water, when surface water is abstracted for drinking water. This gap leads to the consumer risk assessment from the consumption of drinking water being not finalised for all the representative uses.

In the section on **ecotoxicology**, a critical area of concern has been identified for wild mammals, as high long-term risk was identified for all uses of mepanipyrim. Further data gaps were identified in the area of bee risk assessment.

Regarding the assessment of the **endocrine disruption** (ED) properties, based on the available data and assessments, it can be concluded that mepanipyrim meets the ED criteria for humans and wild mammals as non-target organisms according to points 3.6.5 and 3.8.2 of Annex II to Regulation (EC) No 1007/2009, as amended by Commission Regulation (EU) 2018/605.

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## Background

Commission Implementing Regulation (EU) No 844/2012<sup>1</sup> (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<sup>2</sup>. This regulates for the European Food Safety Authority (EFSA) the procedure for organising the consultation of Member States, the applicant(s) and the public on the initial evaluation provided by the rapporteur Member State (RMS) and/or co-rapporteur Member State (co-RMS) in the renewal assessment report (RAR), and the organisation of an expert consultation where appropriate.

In accordance with Article 13 of the Regulation, unless formally informed by the European Commission that a conclusion is not necessary, EFSA is required to adopt a conclusion on whether the active substance can be expected to meet the approval criteria provided for in Article 4 of Regulation (EC) No 1107/2009 within 5 months from the end of the period provided for the submission of written comments, subject to an extension of up to 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, Belgium, and co-RMS, Greece, received an application from K-I Chemical Europe SA/NV for the renewal of approval of the active substance mepanipyrim. Complying with Article 8 of the Regulation, the RMS checked the completeness of the dossier and informed the applicant, the co-RMS (Greece), the European Commission and EFSA about the admissibility.

The RMS provided its initial evaluation of the dossier on mepanipyrim in the RAR, which was received by EFSA on 3 May 2016 (Belgium, 2016).

In accordance with Article 12 of the Regulation, EFSA distributed the RAR to the Member States and the applicant, K-I Chemical Europe SA/NV, for consultation and comments on 12 July 2016. EFSA also provided comments. In addition, EFSA conducted a public consultation on the RAR. EFSA collated and forwarded all comments received to the European Commission on 13 September 2016. At the same time, the collated comments were forwarded to the RMS for compilation and evaluation in the format of a reporting table. The applicant was invited to respond to the comments in column 3 of the reporting table. The comments and the applicant's response were evaluated by the RMS in column 3.

The need for expert consultation and the necessity for additional information to be submitted by the applicant in accordance with Article 13(3) of the Regulation were considered in a telephone conference between EFSA and the RMS on 21 October 2016. On the basis of the comments received, the applicant's response to the comments and the RMS's evaluation thereof, it was concluded that additional information should be requested from the applicant, and that EFSA should conduct an expert consultation in the areas of mammalian toxicology, residues and ecotoxicology.

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

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

A final consultation on the conclusions arising from the peer review of the risk assessment took place with Member States via a written procedure in April 2017, leading to the finalisation of the EFSA Conclusion (EFSA, 2017a).

Commission Regulation (EU) 2018/605<sup>3</sup> introduced new scientific criteria for the determination of endocrine-disrupting (ED) properties, applicable as of 10 November 2018 to all applications for the

<sup>1</sup> 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.

<sup>2</sup> 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.

<sup>3</sup> Commission Regulation (EU) 2018/605 of 19 April 2018 amending Annex II to Regulation (EC) No 1107/2009 by setting out scientific criteria for the determination of endocrine-disrupting properties. OJ L 101, 20.4.2018, p. 33–36.

approval/renewal of active substances, including pending applications. The peer review on the active substance mepanipyrim was already completed at the time of entry into force of the new criteria, and an assessment of the ED potential in line with the ECHA/EFSA guidance (2018) document<sup>4</sup> for this substance was not available.

Since on the basis of the EFSA Conclusion published on 13 June 2017, it was not possible for risk managers to conclude whether or not the active substance mepanipyrim is an endocrine disruptor, on 14 January 2019 the European Commission requested EFSA to re-assess the information and update its Conclusion on the ED potential of the substance in accordance with the new criteria in accordance with the provisions of Article 14(1a) of Commission Regulation (EU) No 844/2012, as amended by Commission Regulation (EU) 2018/1659. For this purpose, EFSA has performed an assessment of the ED properties of the active substance mepanipyrim in line with the EFSA/ECHA (2018) guidance for further consideration in the peer review (EFSA, 2019), and distributed it to the Member States and the applicant, K-I Chemical Europe SA/NV, for consultation and comments on 28 May 2019.

Following a consultation with Member States in the Pesticide Peer Review Experts' Meeting TC 10 Mammalian toxicology – Ecotoxicology joint session (July 2019), it was concluded that mepanipyrim does not meet the ED criteria for humans for the thyroid (T) modality according to point 3.6.5 of Annex II of Regulation (EC) No 1107/2009, as amended by Commission Regulation (EU) No 2018/605. However, additional testing was required to complete the data package for the oestrogen, androgen and steroidogenesis (EAS)-modalities in relation to human health and to further investigate the ED properties of the substance for non-target organisms. Therefore, in accordance with the provisions of Commission Regulation (EU) No 2018/1659<sup>5</sup>, on 9 August 2019, the applicant was given the opportunity to submit, within a period of 30 months, additional information to address the approval criteria set out in points 3.6.5 and 3.8.2 of Annex II to Regulation (EC) No 1107/2009, as amended by Commission Regulation (EU) No 2018/605, and/or documentary evidence demonstrating that mepanipyrim may be used such that exposure is negligible, and/or the conditions for application of the derogation under Art.4(7) of Regulation (EC) No 1107/2009 are met. The additional information submitted by the applicant on 7 February 2022 was subsequently evaluated by the RMS. EFSA received the updated RAR with the revised ED assessment from the RMS on 14 June 2022 (Belgium, 2022).

A consultation on the revised RAR on the ED assessment made available by the RMS after the 30-month clock stop was conducted with Member States, the applicant, EFSA and the public in July–September 2022. All comments received were collated in the format of a reporting table and were considered during the finalisation of the peer review. In addition, in light of the comments received, an ad hoc experts' consultation with Member States at the Pesticides Peer Review Experts' TC 100 and 104 in mammalian toxicology and ecotoxicology on ED was conducted in April 2023.

A final consultation on the updated conclusion arising from the peer review following the mandate from the European Commission took place with Member States via a written procedure in June–July 2023.

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 mepanipyrim as a fungicide on table and wine grapes and in field and protected strawberries and tomatoes, as proposed by the applicant. In addition, the conclusions were updated with regard to the endocrine-disrupting properties of mepanipyrim following the mandate received from the European Commission on 14 January 2019. A list of the relevant end points for the active substance and the formulation for representative uses is provided in Appendix A.

In addition, a key supporting document to this updated conclusion is the Peer Review Report (EFSA, 2017, updated in July 2023), 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:

<sup>4</sup> ECHA (European Chemicals Agency) and EFSA (European Food Safety Authority) with the technical support of the Joint Research Centre (JRC), Andersson N, Arena M, Auteri D, Barmaz S, Grignard E, Kienzler A, Lepper P, Lostia AM, Munn S, Parra Morte JM, Pellizzato F, Tarazona J, Terron A and Van der Linden S, 2018. Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009. EFSA Journal 2018;16(6):5311, 135 pp. <https://doi.org/10.2903/j.efsa.2018.5311>. ECHA-18-G-01-EN.

<sup>5</sup> Commission Implementing Regulation (EU) 2018/1659 of 7 November 2018 amending Implementing Regulation (EU) No 844/2012 in view of the scientific criteria for the determination of endocrine disrupting properties introduced by Regulation (EU) 2018/605. OJ L 278, 8.11.2018, p. 3–6.

- the comments received on the RAR;
- the reporting tables (21 October 2016 and January 2023<sup>6</sup>);
- the evaluation table (8 May 2017, updated in July 2023);
- 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 EFSA endocrine disruption (ED) assessment (May 2019)<sup>7</sup>
- the comments received on the draft EFSA conclusion.

Given the importance of the RAR, including its revisions (Belgium, 2017, 2022, 2023), and the Peer Review Report and the EFSA ED assessment (EFSA, 2019), all these 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

Mepanipyrin is the ISO common name for *N*-[4-methyl-6-(prop-1-ynyl)pyrimidin-2-yl]aniline (IUPAC).

The formulated product for the representative uses in the context of the evaluation was 'Frupica 50 WP', a wettable powder in sealed water soluble bag (WP-SB), containing 500 g/kg mepanipyrin.

The representative uses evaluated were foliar spray applications for the control of grey mould *Botryotinia fuckeliana* (BOTRCI) in table and wine grapes and in field and protected strawberries and tomatoes, in the Southern European zone. Full details of the GAPS can be found in the list of end points in Appendix A.

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

## Conclusions of the evaluation

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

The following guidance documents were followed in the production of this conclusion: SANCO/3029/99-rev. 4 (European Commission, 2000a), SANCO/3030/99-rev. 4 (European Commission, 2000b), SANCO/10597/2003-rev. 10.1 (European Commission, 2012), SANCO/825/00-rev. 8.1 (European Commission, 2010).

The new proposed reference specification for mepanipyrin is based on batch data from industrial scale production and also on QC data for the relevant impurity. The minimum purity of the technical material is 970 g/kg. There is no FAO specification available for mepanipyrin. Toluene is considered a relevant impurity, however of no toxicological concern at the level specified (maximum 5 g/kg). The batches used in the toxicological and ecotoxicological assessments support the proposed renewal specification. The initial reference specification for first approval was considered to be not entirely covered by the toxicological studies. As a consequence, it is recommended to update the reference specification of the first approval.

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

The methods for the generation of pre-approval data required for the risk assessment were adequately addressed. HPLC-UV methods are available for the determination of mepanipyrin in the technical material and in the representative formulation and for the determination of the respective

<sup>6</sup> Reporting Table following consultation on the revised RAR on the assessment of the endocrine disrupting properties made available after the 30-month clock stop.

<sup>7</sup> ED assessment performed by EFSA before the timepoint of the ED additional information request (stop of the clock). The ED assessment including evaluation of the newly provided additional information on the endocrine disruption properties following the ED clock stop is available in the revised RAR (Belgium, 2023) with the final outcome presented in the current EFSA Conclusion (see Section 6).



impurities in the technical material. CIPAC MT 198 can be used for the determination of toluene in the formulation.

Mepanipyrim residues can be monitored in food and feed of plant origin by the QuEChERS method using LC–MS/MS with LOQs of 0.01 mg/kg in acidic, dry and high water content matrices and by gas chromatography (GC) with an LOQ of 0.01 mg/kg in oily matrices.

An analytical method for food of animal origin is not required due to the fact that no residue definition is proposed.

Adequate LC–MS/MS or GC–MS methods are available for monitoring residues of mepanipyrim in soil with an LOQ of 0.01 mg/kg. Mepanipyrim residues can be determined in drinking water by LC–MS/MS with an LOQ of 0.05 µg/L while in surface water by GC–MS with an LOQ of 0.1 µg/L. Monitoring mepanipyrim in air can be done by GC–MS with an LOQ of 0.75 µg/m<sup>3</sup>.

A **data gap** was identified for a method for monitoring mepanipyrim in body fluids and tissues.

## 2. Mammalian toxicity

The toxicological profile of the active substance mepanipyrim and its metabolites was discussed at the Pesticides Peer Review Experts' Meeting 151 (February 2017) and assessed based on the following guidance documents: SANCO/221/2000-rev. 10-final (European Commission, 2003), SANCO/10597/2003-rev. 10.1 (European Commission, 2012), Guidance on dermal absorption (EFSA PPR Panel, 2012) and Guidance on the application of the CLP Criteria (ECHA, 2015).

A number of significant impurities were reported for mepanipyrim. The toxicological assessment covers the technical specification. Toluene is a relevant impurity due to its hazard classification. However, the maximum toluene level proposed for the technical specifications is not of toxicological concern. The relevance of two other impurities reported cannot be assessed due to lack of adequate information regarding their toxicological profile (**data gap**).

Mepanipyrim absorption is rapid and extensive (higher than 80%). Mepanipyrim is mainly distributed in fat, skin, kidney, adrenals, thyroid and liver. More than 90% of mepanipyrim is excreted within 48 h, mostly through faeces and bile. The kinetics pattern between the low and high dose is similar, with excretion through urine being slightly delayed for the high dose. Mepanipyrim is extensively metabolised in the rat via oxidations, hydroxylations and glutathione substitutions. Unchanged parent is only observed in faeces. Comparative interspecies metabolism study *in vitro* has not been provided and consequently the kinetics investigation remains open (**data gap – issue not finalised**).

Low **acute toxicity** was observed when mepanipyrim was administered by the oral, dermal or inhalation routes; no skin irritation, very slight eye irritation and no potential for skin sensitisation were attributed to the active substance. Since mepanipyrim was found to be phototoxic *in vitro*, and there is currently no validated test *in vivo*, the phototoxic and photomutagenic potential of the substance could not be finalised.

As regards **short-term toxicity**, in the 90-day rat study, critical effects observed were related to haematology (decrease of the mean corpuscular haemoglobin concentration (MCHC) and lymphocytes in males, increase of neutrophils in males), and clinical chemistry findings (increase of cholesterol, decrease of triglyceride and decrease of the non-esterified fatty acids) leading to a no observed adverse effect level (NOAEL) of 6.95 mg/kg body weight (bw) per day. In the 13-week study in mice, the NOAEL was 19 mg/kg bw per day due to liver hypertrophy. In dogs, the critical effects were liver hypertrophy and prostate atrophy in both 90-day and 1-year dog study leading to NOAELs of 7.5 mg/kg bw per day and 2.5 mg/kg bw per day, respectively. Liver hypertrophy was observed also in the 28-day dermal study in rabbit with the NOAEL in the 300 mg/kg bw per day.

The **genotoxic potential** of mepanipyrim was fully tested (Ames test, *in vitro* chromosomal aberrations (CA) in Chinese hamster ovary (CHO), and *in vivo* CA and micronucleus (MN) test) and the results were discussed in the experts' meeting. Overall, it was agreed that mepanipyrim is unlikely to be genotoxic.

The findings of the **long-term carcinogenicity** rat study (2 years) were discussed in the experts' meeting concluding on a long-term low-observed adverse effect level (LOAEL) of 2.45 mg/kg bw per day due to pancreas atrophy in males and non-relevance of the hydrometra. The long-term NOAEL set for the respective mice study was at 56 mg/kg bw per day. Based on the liver adenomas, cystadenomas and marginal uterine carcinomas observed in rats and the liver adenomas and carcinomas observed in mice, the experts proposed to maintain the harmonised classification of mepanipyrim for carcinogenicity category 2. Some experts considered that the criteria for classification

according to Regulation (EC) No 1272/2008 for the category 1B might be met. Regarding the mechanism of carcinogenicity, the experts considered that in the absence of a genotoxic potential, an initiating potential of mepanipyrin is not considered plausible.

Two main two-generation **reproductive** studies in rats were submitted for mepanipyrin. The LOAEL for parental and offspring's toxicity is set at 2.45 mg/kg bw per day based on the observed increased incidence of centrilobular hepatocytic fatty vacuolation. Also, the NOAEL for reproduction is set at 2.45 mg/kg bw per day due to increased incidence of extended oestrus cycle. Two main **developmental** studies (one in rats and one in rabbits) were submitted for mepanipyrin. The NOAEL for maternal toxicity in rats set at 150 mg/kg bw per day based on a greater than 10% decrease of the body weight gain observed at the 750 mg/kg bw per day. The NOAEL for maternal toxicity in rabbits is set at 10 mg/kg bw per day based on few faeces in under-tray. The overall NOAEL for development is set at 10 mg/kg bw per day based on resorptions and post-implantations in rabbits observed at 30 mg/kg bw per day. The experts considered that there is no need for classification regarding developmental toxicity.

The **neurotoxicity** of mepanipyrin was studied through an acute study. Clinical signs and decrease of rearing and activity counts were observed in the two higher doses in the absence of histopathological examination. An acute NOAEL for neurotoxicity was set at 80 mg/kg bw.

The **acceptable daily intake** (ADI) and **acceptable operator exposure level** (AOEL) are set at 0.012 mg/kg bw per day based on the 2-year study and two-generation reproductive toxicity study LOAELs of 2.45 mg/kg bw per day, and an uncertainty factor (UF) of 200 (two for the use of a LOAEL instead of a NOAEL and 100 as the standard UF). The **acute reference dose** (ARfD) and **acute acceptable operator exposure level** (AAOEL) are set at 0.1 mg/kg bw based on the NOAEL of 10 mg/kg bw per day from the rabbit developmental study and a UF of 100. The newly set reference values (TRVs) constitute a revision of those set during the first peer review (ADI = 0.024 mg/kg bw per day, ARfD = 0.30 mg/kg bw and AOEL = 0.07 mg/kg bw per day) (European Commission, 2004). Following the updated assessment of the endocrine-disrupting potential, the newly set TRVs are protective towards the pattern of EAS-related effects observed in the available data set; the lowest observed adverse effect level (LOAEL), where EAS-mediated adversity was observed in females (P and F1 generation) in the form of increased incidence of extended oestrus cycle, is 7.33 mg/kg bw per day from a two-generation toxicity study in rats (see Section 6).

The RMS estimated **non-dietary exposure** (i.e. operator, worker, bystander and resident) with dermal absorption values derived from an *in vitro* dermal absorption study on human skin, i.e. 0.4% for the concentrate, 6% for in-use field dilutions for low volume applications and 13% for high volume applications. Using these dermal absorption values and based on the AOEL of 0.012 mg/kg bw per day, the operator exposure exceeds the AOEL, even when personal protective equipment (PPE) is used, in the cases of (a) vine crops high volume field application with tractor-mounted broadcast air-assisted sprayer (estimated as 141% of the AOEL in the less conservative case of German model with the use of PPE (gloves), coverall and sturdy footwear), and (b) of low volume hand-held knapsack application, indoors, to strawberry or tomato (105% of the AOEL, Dutch indoor model, additional PPE including gloves). For all other scenarios, PPE should be used to ensure that operator exposure does not exceed the AOEL. Estimated worker exposure exceeds the AOEL, even with PPE, in the case of re-entry in vine crops for harvesting and crop inspection (estimated as 115 and 130% of the AOEL, respectively). PPE should be used to ensure that workers exposure in tomatoes and strawberries does not exceed the AOEL. Bystanders' and residents' exposure is below AOEL in all cases.

The **metabolite** M31 was found in significant amounts in plant residues while no ground water metabolites were identified. In addition, the metabolites M33 and M36 were identified in lower levels (see Section 3); therefore, the toxicological profile of M31, M33 and M36 was discussed during the experts' meeting. It was agreed that their genotoxic potential can be considered covered by the parent and by the metabolite M11, for which a full set of genotoxicity tests is available, as the structural differences are not considered related to alteration of the genotoxic potential of these chemicals. However, the same argument is not applicable for other toxicity endpoints, and consequently, the reference values of the parent compound cannot be applied to M31. For this reason, QSAR data and repeated dose toxicity data should be provided for the metabolite M31 (main metabolite) (**data gap**). The same data would cover metabolites M33 and M36.

### 3. Residues

The assessment in the residue section is based on the OECD guidance document on overview of the residue chemistry studies (OECD, 2009), the OECD publication on the maximum residue level (MRL) calculations (OECD, 2011) the European Commission guideline document on the MRL setting (European Commission, 2011).

Mepanipyrim was discussed at the Pesticide Peer Review Expert Meeting 153 in February 2017.

Metabolism of mepanipyrim in primary crops was investigated upon foliar application on fruit (grapes, tomatoes and apples) with the parent compound <sup>14</sup>C-labelled either on the aniline or on the pyrimidine moiety. The experimental designs were in compliance with the representative uses for the total dose rates representing 1.9 N rate when compared to the EU GAPs for strawberries and tomatoes and 2.5 N for table grapes, while the harvest interval was longer (30–32 days for apples and grapes and 62 days for tomatoes) compared to the representative GAPs with one day PHI for tomatoes and strawberries and 21 days for grapes. Although, a small deficiency of the metabolism study design was identified, it is not expected to influence the final outcome on the metabolic pattern of mepanipyrim. Therefore, the metabolism studies in plant are considered reliable.

The parent mepanipyrim was found to be the predominant compound of the total residues in all crops (23–70% total radioactive residues (TRRs)). M31 was recovered at significant levels in grapes only and mainly under its conjugated form (20–30% TRR) while it occurred at very low proportions in tomato and apple ( $\leq 1\%$  TRR). Other minor metabolites (M33, M36) were also identified but accounted for low levels ( $< 3\%$  TRR) in the investigated crops. It is noted that the metabolic pattern of mepanipyrim in fruit crops was confirmed in the GAP-compliant residue trials on grapes and strawberries where significant residue levels of M31 were recovered (0.22 mg/kg and 0.32 mg/kg, respectively) while this compound was not detected in the tomato residue trials ( $< 0.01$  mg/kg).

The **residue definition for enforcement purposes** was defined as mepanipyrim only. For risk assessment and considering that the toxicological profile of M31 was not fully addressed (see data gap in Section 2), the **residue definition for risk assessment** was proposed as mepanipyrim and M31 (free and conjugated). The way the risk assessment residue definition will be expressed is pending upon the requested toxicity profile of M31. The proposed residue definitions are limited to fruit crops only.

Based on the confined rotational crop metabolism study conducted at the target application rate (1 N), the same residue definitions as for the primary crops are applicable. No residues are expected to be present in rotational crops, provided that mepanipyrim is applied according to the representative uses.

Under the standard hydrolysis conditions representative of food processing, mepanipyrim residues were found to be stable. Moreover, in view of the significant residue levels of M31 recovered in the GAP-compliant field residue trials on grapes and strawberry, the experts were of the opinion that the fate of M31 under the standard processing conditions should also be investigated (**data gap**). Since the nature of M31 under hydrolysis conditions was not addressed and considering the chemical structure of M31, further data should be submitted to exclude potential degradation of M31 leading to the formation of aniline. Meanwhile, the residue definition for processed commodities cannot be concluded.

A sufficient number of residue trials are available, respectively, for table and wine grapes and for strawberries, while for tomatoes one additional residue trial compliant with the indoor GAP is requested (**data gap**). All the trials were analysed for mepanipyrim and M31 residues and they are supported by validated analytical methods and acceptable storage stability data where residues of mepanipyrim and M31 are shown to be stable for at least 18 months in high-acid and high-water content commodities, in processed commodities; and for 9 months in high-starch commodities. Processing studies were submitted on strawberries, tomatoes and grapes, and processing factors were derived for several processed commodities. It is, however, highlighted that the validity of the derived processing factors should be reconsidered upon the outcome of the identified data gap to address the behaviour of M31 under the standard hydrolysis conditions for processing. Conversion factors from monitoring to risk assessment were derived from the residue trials of grapes (1.6) and strawberries (1.1) assuming that the toxicological reference values set for the parent compound are applicable also to metabolite M31 (pending submission of the toxicological data for M31).

Having regard to the representative uses, a livestock exposure assessment is not triggered.

For the time being, the consumer risk assessment has to be regarded as provisional considering the outstanding data to finalise the residue definitions in primary crops and in processed commodities.

Pending the outcome on the toxicological profile of M31, an indicative consumer risk assessment has been conducted for parent mepanipyrim by using the EFSA PRIMo rev.2 model.<sup>8</sup> Long-term or short-term intake concerns were not identified for the consumers since the highest chronic and highest acute intakes accounted for 15% ADI (WHO Cluster diet B) and 76% ARfD (table grapes). Furthermore, a preliminary consumer risk assessment has been conducted considering the exposure to the sum of mepanipyrim and M31 (free and conjugated). Assuming for M31 the same toxicity as for the parent and using the HR and supervised trials median residue (STMR) values derived from the residue field trials for table and wine grapes, strawberries and tomatoes, acute and chronic intakes concern were not identified (max IESTI: 82% ARfD for table grapes and max IEDI 16% of ADI, FR all population). However, it should be highlighted that this risk assessment is provisional only.

It is noted, that in the framework of the peer review of mepanipyrim, the toxicological reference values were lowered (see Section 2) and the inclusion of M31 in the residue definition for risk assessment was proposed. Pending the final decision on the expression of the risk assessment residue definition, the established MRLs under Article 12 of Regulation (EC) No 396/2005 and the overall consumer exposure and risk assessment might need to be revised (EFSA, 2011).

The data requirement for the determination of the residue levels of mepanipyrim and M31 in pollen and bee products for human consumption resulting from residues taken up by honeybees at blossom from grapes, field grown strawberries and field grown tomatoes was not addressed (**data gap**).

#### 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, mepanipyrim exhibited moderate to high persistence. No major (> 10% applied radioactivity (AR)) metabolites were formed. Mineralisation of the pyrimidine ring <sup>14</sup>C radiolabel to carbon dioxide accounted for 2.4–14.2% AR after 120 days and mineralisation of the phenyl ring <sup>14</sup>C radiolabel to carbon dioxide accounted for 5.4% AR after 120 days. The formation of unextractable residues (not extracted by acetonitrile/water) for the pyrimidine ring <sup>14</sup>C radiolabel accounted for 18.6–67.7% AR after 120 days and for the phenyl ring <sup>14</sup>C radiolabel accounted for 26.0% AR after 120 days. In anaerobic soil incubations and in photolysis studies, degradation of mepanipyrim was slow and no major (> 10% applied radioactivity (AR)) metabolites were formed.

Mepanipyrim exhibited medium to slight mobility or was immobile in soil; adsorption is not expected to be pH dependent.

In satisfactory field dissipation studies carried out at four different sites: one in the Netherlands, one in France, one in Spain and one in Italy (spray application to the soil surface on bare soil plots in spring), mepanipyrim exhibited moderate to medium persistence. Field study DegT50 values for modelling were derived following normalisation to FOCUS reference conditions (20°C and pF2 soil moisture) following the EFSA (2014) DegT50 guidance. When deriving the modelling endpoint in the Spanish field study, only three data points were available, and so this study was not considered when calculating the geometric mean DT50. Consequently, as only three normalised DT50 values were available from the field dissipation studies, following EFSA (2014) DegT50 guidance all the laboratory and field DT50 values were pooled to derive the geometric mean DT50 to be used in future modelling. The field data endpoints were not combined with lab values to derive modelling endpoints. Column leaching studies were carried out for mepanipyrim. Radioactivity in the leachates was very low (< 0.134% AR) and no metabolites were formed.

In laboratory incubations in dark aerobic natural sediment water systems, mepanipyrim exhibited moderate persistence; no major metabolites were formed. The unextractable sediment fraction (not extracted by acetonitrile/water) was the major sink for the pyrimidine ring <sup>14</sup>C radiolabel, accounting for 84.3% AR at study end (100 days). Mineralisation of this radiolabel accounted for 5.5–14.6% AR at the end of the study. The rate of decline of mepanipyrim in a laboratory sterile aqueous photolysis experiment was slow relative to that occurred in the aerobic sediment water incubations. No chromatographically resolved component (excluding mepanipyrim) accounted for > 10% AR. A **data gap** was identified for studies on aerobic mineralisation in surface water. However, the available information on sediment water systems was sufficient for use in exposure modelling for the edge of field surface water bodies.

<sup>8</sup> In line with the agreed approach on implementation of the PRIMo model rev.3.1, in April 2020, the consumer risk assessment by using PRIMo rev 3.1 was also conducted by the RMS (see the List of Endpoints in Appendix A and revised RAR (Belgium, 2023)).

The necessary surface water and sediment exposure assessments (Predicted environmental concentrations (PEC) calculations) were carried out for mepanipyrim, using the FOCUS (FOCUS, 2001) Step 1 and Step 2 approach (version 3.2 of the Steps 1–2 in FOCUS calculator). Furthermore, appropriate Step 3 (FOCUS, 2001) and Step 4 calculations were available.<sup>9</sup> The Step 4 calculations appropriately followed the FOCUS (FOCUS, 2007) guidance, with no-spray drift buffer zones of up to 20 m being implemented for the drainage scenarios (representing a 91–93% spray drift reduction), and combined no-spray buffer zones with vegetative buffer strips of up to 20 m (reducing solute flux in run-off by 80% and erosion runoff of mass adsorbed to soil by 95%) being implemented for the run-off scenarios. The SWAN tool (version 4.0.1) was appropriately used to implement these mitigation measures in the simulations. However, risk managers and others may wish to note that while run-off mitigation is included in the Step 4 calculations available, the FOCUS (FOCUS, 2007) report acknowledges that for substances with  $K_{Foc} < 2,000$  mL/g (i.e. mepanipyrim), the general applicability and effectiveness of run-off mitigation measures had been less clearly demonstrated in the available scientific literature, than for more strongly adsorbed compounds. At Step 4, the deposition following volatilisation from plant surfaces was calculated using the EVA 2.0 model.

The representative protected uses (in strawberries and tomatoes) have been assessed as being covered by the exposure assessment performed for open field uses. Protected cropping systems were not considered limited to permanent greenhouses.

The necessary groundwater exposure assessments were appropriately carried out using FOCUS (European Commission, 2014a) scenarios and the models PEARL 4.4.4, PELMO 4.4.3 and MACRO 5.5.3.<sup>9</sup> The potential for groundwater exposure from the representative uses by mepanipyrim above the parametric drinking water limit of 0.1 µg/L was concluded to be low in geoclimatic situations that are represented by all nine FOCUS groundwater scenarios.

The applicant did not provide appropriate information to address the effect of water treatments processes on the nature of the residues that might be present in surface water, when surface water is abstracted for drinking water. This has led to the identification of a **data gap** (see Section 7) and results in the consumer risk assessment not being finalised (see Section 10.1).

The PEC in soil, surface water, sediment 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 (2009), EFSA PPR Panel (2013) and EFSA (2013). According to Regulation (EU) No. 283/2013<sup>10</sup>, data should be provided regarding the acute and chronic toxicity to honeybees and data to address the development of honeybee brood and larvae. As the European Commission (2002a) does not provide a risk assessment scheme which is able to use the chronic toxicity data for adult honeybees and the honeybee brood, when performing the risk assessment according to European Commission (2002a), the risk to adult honeybees from chronic toxicity and the risk to bee brood, could not be finalised due to the lack of a risk assessment scheme. Therefore, the EFSA (2013) was used for risk assessment in order to reach a conclusion for the representative uses.

Mepanipyrim was discussed at the Pesticide Peer Review Expert Meeting 154 in February 2017.

Based on the available data and risk assessment, a low acute risk via dietary exposure to **birds** and **wild mammals** was concluded for all representative uses of mepanipyrim. A low long-term risk was also concluded for birds at the Tier I for all the representative uses. A high long-term risk was identified at the Tier I for small herbivorous mammal (all representative uses) and for frugivorous mammal (uses on tomato). At the Pesticide Peer Review Meeting 154 (February 2017), the experts agreed that the available information was not sufficient for supporting the selection of any specific focal species. Therefore, no refinement based on available ecological data could be used in the risk assessment.

Residue data were available for tomato fruits. However, the incorporation of those data ( $n = 9$ ) into the larger data set already available for default residue per unit dose (RUD) estimation ( $n = 86$ ) would not change the outcome of the risk assessment. Considering all the above, a **data gap** was identified for the scenarios where high long-term risk to wild mammals was identified at the tier I. A low risk for

<sup>9</sup> Simulations utilised the agreed Q10 of 2.58 (following EFSA, 2008) and Walker equation coefficient of 0.7.

<sup>10</sup> 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, 1–84.

both birds and mammals was concluded from secondary poisoning and from exposure via contaminated water.

No specific PEC calculations were available for the uses in protected crops, where upward spraying is allowed. The RMS in the RAR has concluded that, in lack of specific calculations, PEC<sub>sw</sub> (up to step 3) for open field downward applications cover for uses in permanent structures, but not necessarily for uses in non-permanent structures. However, considering the kind of application in protected structure (hand-held knapsack sprayer), EFSA concluded that the PEC<sub>sw</sub> for open field uses would represent a worst case (see Section 4); therefore, the risk assessment for all uses in protected structures is considered covered by the analogues uses in the open field. The Tier I acute RAC for **aquatic organisms** was based on the effects to invertebrates, while the chronic RAC was based on the effects seen on fish. Based on PEC calculation with FOCUS Step 3, a high acute and chronic risk was identified in some scenarios for each of the representative uses of mepanipyrim. PEC calculated at the FOCUS Step 4, considering mitigation measures equivalent to 20 m no-spray buffer (uses on vines) and 20 m no-spray buffer and vegetated filter strip (uses on tomato and strawberries) were sufficient to demonstrate a low acute and chronic risk for all scenarios in all representative uses.

The RMS has assessed the risk to **honeybees** in accordance with both European Commission (2002a) and EFSA (2013). A low acute risk (oral and contact) was concluded for all the representative uses of mepanipyrim. A low risk was also concluded for honeybee larvae. Based on Tier I calculations, a low chronic risk was also concluded for all representative uses of mepanipyrim, with the only exception of the treated crop scenario for side upward application on strawberry in non-permanent protected structures. However, considering that: (i) the trigger was only slightly breached; (ii) the exposure toxicity ratio (ETR) was based on a 'greater than' LDD<sub>50</sub> value; (iii) only 4% mortality was observed at the highest tested dose determining the LDD<sub>50</sub> value, a low risk was concluded also for the scenario where the trigger was breached. A low risk for honeybees (acute, chronic and larvae) was concluded at the screening step for consumption of contaminated water. No assessment was available for sublethal effects (**data gap**). No assessment for accumulative effects was available. However, due to the lack of effects observed in the available chronic studies, accumulative effects are not likely to occur. No information was available regarding plant metabolites occurring in pollen and nectar. Therefore, a **data gap** was identified.

Acute (contact and oral) toxicity data were available for **bumblebees**. The RMS has performed the risk assessment in accordance with EFSA (2013). A low acute risk was concluded for contact exposure at the screening step (all uses). Based on Tier I calculations, a low acute oral risk was also concluded for all representative uses of mepanipyrim, with the exception of the treated crop scenario on strawberry (application in open field and in non-permanent protected structures). However, the triggers were only slightly breached, and the LD<sub>50</sub> was a 'greater than' value derived from a test where 0% mortality was recorded at the highest tested dose. For these reasons, a low oral acute risk to bumblebees was concluded for all representative uses of mepanipyrim.

No data were available for **solitary bees**.

Tier I data were available for six species of **non-target arthropods**. The risk assessment based on mortality data from these studies was sufficient for demonstrating a low risk. However, as effects on reproduction were seen on *Aphidius rhopalosiphi* and other two non-standard species, higher tier tests were carried out, including three extended laboratory studies, one semi-field and one field study. Based on such higher tier data, the conclusion of low risk was further supported.

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

## 6. Endocrine disruption properties

The assessment of the endocrine disruption (ED) potential of mepanipyrim was initially discussed at the Pesticides Peer Review Experts' Teleconference TC 10 (Mammalian Toxicology – Ecotoxicology joint session) in July 2019.

It was agreed that additional testing was required to complete the data package for the oestrogen, androgen and steroidogenesis (EAS)-modalities in relation to **human health** and to further investigate the ED properties of the substance for **non-target organisms**.<sup>11</sup>

<sup>11</sup> Pesticide Peer Review Meeting PREV 10 (July 2019; EFSA, 2023).

In the context of the mandate from the European Commission and following submission of additional information on the ED potential by the applicant during a 30-month stop of the clock, mepanipyrin was further discussed at the Pesticides Peer Review Experts' TC 100 and 104 (April 2023) for both humans and non-target organisms.

With regard to the assessment of the endocrine disruption (ED) potential of mepanipyrin **for humans** according to the ECHA/EFSA guidance (2018), in determining whether mepanipyrin interacts with the oestrogen, androgen and steroidogenesis (EAS) and thyroid (T)-mediated pathways, the number and type of effects induced and the magnitude and pattern of responses observed across studies were considered. Additionally, the conditions under which effects occur were considered, in particular, whether or not endocrine-related responses occurred at dose(s) that also resulted in overt toxicity. The assessment is therefore providing a weight of evidence (WOE) analysis of the potential interaction of mepanipyrin with the EAS and T signalling pathways using the available evidence in the data set.

The data set for the **T-modality** was considered complete and T-mediated adversity was not identified. Therefore, based on the available and sufficient data set, it was concluded that the ED criteria are not met for the T-modality (**Scenario 1a** of the EFSA/ECHA (2018) ED Guidance).

In line with the EFSA/ECHA ED guidance (2018), the data set for the **EAS**-modalities was not considered complete. Positive endocrine activity was reported in the steroidogenesis assay (i.e. induction of E2 synthesis) and equivocal results were reported in the aromatase assay. In line with the EFSA/ECHA ED Guidance (2018) and with the recommendation of the peer review expert consultation in 2019,<sup>12</sup> a level 5 study should have been conducted during the stop of the clock to enable a conclusion on the ED-mediated adversity. However, a level 5 study was not carried out, and the experts confirmed that the execution of the OECD TG 443 test would have been the appropriate test to conclude on the ED criteria and to clarify the potential adverse consequence of a positive endocrine activity, as observed in the level 2 studies.

In the absence of such data, the experts agreed that a higher level of uncertainty should be accepted to conclude on the ED criteria. Therefore, the lines of evidence of adversity for both 'EAS-mediated' and 'Sensitive to, but not diagnostic of EAS' parameters, with the inclusion of the positive endocrine activity, were considered in the WoE analysis and discussed at the Pesticides Peer Review Experts' meeting<sup>13</sup> and at the EFSA endocrine disruptor (ED) working group. The inclusion of the sensitive parameters in the WoE analysis, which is generally not necessary when the dataset is complete, was deemed appropriate to compensate the lack of the EAS-mediated endpoints requested, but not investigated, in the updated dataset of studies on mepanipyrin after the 30 months stop of the clock.

A pattern of EAS-mediated adversity was observed, and it is substantiated in the available data set by histopathological changes in the testicular seminiferous epithelium in male rats, deregulation in oestrus cycle in female rats, ovarian follicular cysts in female rats, decrease of prostate weight in male dogs and occasional occurrence in female rats of uterine endometrial hyperplasia, hydrometra and uterine adenocarcinoma, which were reported in studies of different duration. Moreover, perturbation of the EAS pathways was complemented by changes in 'Sensitive to, but not diagnostic of EAS' endpoints i.e. decrease in the fertility index and increased number of abortions and post-implantation loss observed in a two-generation toxicity study in rats and in the developmental toxicity study in rabbit.

In the studies conducted with mepanipyrin, the lowest observed adverse effect level (LOAEL), where EAS-mediated adversity was observed in females (P and F1 generation) in the form of increased incidence of extended oestrus cycle, is 7.33 mg/kg bw per day from a two-generation toxicity study in rats. A **no observed adverse effect level (NOAEL)** for reproductive toxicity of **2.45 mg/kg bw per day** can be therefore derived.

On this basis, considering the adverse effects observed in the EAS-mediated and in the 'Sensitive to, but not diagnostic of EAS' endpoints and the positive outcome in the endocrine activity, the experts agreed that a plausible mode of action (MoA) dealing with an increase in circulating level of oestradiol as intermediate key event (KE) can be postulated. Indeed, several adverse outcomes (in line with the EAS-mediated and sensitive endpoints affected in the mepanipyrin dataset) can be consequent of this KE (see e.g.: EFSA PPR Panel, 2023. *Scientific Opinion on the development of adverse outcome*

<sup>12</sup> Pesticide Peer Review Meeting PREV 10 (July 2019; EFSA, 2023).

<sup>13</sup> See expert consultation point 2.13 of the Pesticide Peer Review Experts' TC 100 (April 2023; EFSA, 2023).

pathways relevant for the identification of substances having endocrine disruption properties. Uterine adenocarcinoma as adverse outcome).

Based on the WoE and uncertainty analysis,<sup>14</sup> it was concluded at the Peer Review Experts' meeting that the **ED criteria were met** for the **EAS-modalities (Scenario 2b)** of the ECHA/EFSA (2018) ED Guidance), leading to a critical area of concern (see Section 10.2). This decision was in line with the advice given by the EFSA ED working group.

The outcome of the assessment reported above for humans also applies to **wild mammals as non-target organisms**, with regard to **the T-modality**. With regard to the **EAS-modalities**, the population relevance of the EAS-mediated adverse effects observed in mammals was discussed at the Peer Review Experts' meeting.<sup>15</sup> It was agreed that the majority of the effects observed were adverse for wild mammal populations, and therefore, **the conclusion drawn for humans also applies to wild-mammals as non-target organisms for the EAS-modalities**, leading to a critical area of concern (see Section 10.2).

**For non-target organisms other than mammals**, an amphibian metamorphosis assay (AMA, OECD TG 231) and a fish short-term reproductive assay (FSTRA, OECD TG 229) were available for the assessment of the T- and EAS-modalities, respectively. The reliability and the findings of both the AMA and FSTRA studies were discussed at the Peer Review Experts' meeting.<sup>16</sup> For the AMA study, it was agreed that (i) the study was reliable, and that, owing to the way the results were reported (ii) it could not be ruled out whether the changes observed in the thyroid histopathology (i.e. increased prevalence and severity of follicular cell hypertrophy and hyperplasia) were an indication of a disruption of the hypothalamic–pituitary–thyroid (HPT) axis. Additional information would be needed to reach a more robust conclusion for the assessment of the T-modality for non-target organisms other than mammals.<sup>17</sup>

For the FSTRA study, it was agreed that although some reliability issues were identified, the study results were not considered indicative of a pattern of endocrine activity through the EAS-modalities. Therefore, although some uncertainties remain, it can be considered likely that mepanipyrim does not meet the ED criteria for the EAS-modalities for non-target organisms other than mammals.

**Overall**, based on the above-mentioned assessments, mepanipyrim meets the ED criteria for humans and wild mammals as non-target organisms for the EAS-modalities as laid down in points 3.6.5 and 3.8.2 of Annex II to Regulation (EC) No 1107/2009, as amended by Commission Regulation (EU) 2018/605 (critical area of concern, see Section 10.2).

<sup>14</sup> See Appendix 2 of the Pesticides Peer Review Experts' TC 100 (April 2023; EFSA, 2023).

<sup>15</sup> See expert consultation point 5.4 of the Pesticides Peer Review Experts' TC 104 (April 2023; EFSA, 2023).

<sup>16</sup> See expert consultation points 5.3 and 5.4 of the Pesticides Peer Review Experts' TC 104 (April 2023; EFSA, 2023).

<sup>17</sup> Since mepanipyrim already meets the ED criteria for the EAS-modalities in both humans and NTOs, as laid down in points 3.6.5 and 3.8.2 of Annex II to Regulation (EC) No 1107/2009, as amended by Commission Regulation (EU) 2018/605, no further data are deemed necessary.



## 7. 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
mepanipyrim	Moderate to high persistence	Low risk to soil organisms
	Single first-order and biphasic kinetics DT <sub>50</sub> 38.8–155.8 days (DT <sub>90</sub> 128.9–> 1,000 days; 20°C, 19.6–44.9% water content at pF2)	
	Northern and Southern European field dissipation studies	
	Moderate to medium persistence	
	Single first-order and biphasic kinetics DT <sub>50</sub> 11.8–82.1 days (DT <sub>90</sub> 127–273 days)	

**Table 2:** Groundwater

Compound (name and/or code)	Mobility in soil	> 0.1 µg/L at 1 m depth for the representative uses <sup>(a)</sup>	Pesticidal activity	Toxicological relevance
mepanipyrim	Medium mobility to immobile K <sub>FOC</sub> 395–5,859 mL/g	No	Yes	Yes

(a): FOCUS scenarios or relevant lysimeter.

**Table 3:** Surface water and sediment

Compound (name and/or code)	Ecotoxicology
mepanipyrim	Low risk to organisms living in surface water when mitigation measures are in place

**Table 4:** Air

Compound (name and/or code)	Toxicology
mepanipyrim	Rat LC <sub>50</sub> inhalation > 0.59 mg/L air/4 h (nose only) (no classification required)

## 8. 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 method for monitoring mepanipyrim in body fluids and tissues (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 1).
- The assessment of the toxicological relevance of two impurities in comparison to the toxicological profile of the parent should be provided (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 2).
- Comparative interspecies metabolism study *in vitro* should be provided (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 2).
- QSAR data and repeated dose toxicity data relevant to consumer exposure should be provided for the metabolite M31 (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 2).
- An additional indoor GAP compliant residue trial on tomatoes (relevant for tomato indoor use evaluated; submission date proposed by the applicant: unknown; see Section 3).
- The fate of M31 under the standard processing conditions should be further investigated (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 3).
- Determination of residues as proposed for risk assessment residue definition in pollen and bee products for human consumption, taken up by honeybees from crops at blossom (relevant for grapes, strawberries outdoor use and tomatoes outdoor use; submission date proposed by the applicant: unknown; see Section 3).
- Further information on the effect of water treatment processes on the nature of residues potentially present in surface water, when surface water is abstracted for drinking water (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 4).
- Studies on aerobic mineralisation in surface water should be provided (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 4).
- Further information to refine the long-term risk to wild mammals (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 5).
- Based on EFSA (2013), suitable data to address the risk of sublethal effects to honeybees due to exposure to mepanipyrim (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 5).
- Information to assess the risk to honeybees due to plant metabolites occurring in pollen and nectar (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 5).

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

- PPE has to be used to mitigate the risk for the operators during application (a) of low volume on vines, and (b) outdoor on strawberry or tomato (see Section 2).
- PPE has to be used during harvesting strawberry or tomato to mitigate the risk for the worker (see Section 2).
- Measures equivalent to 20 m no-spray buffer (uses on vines) and 20 m no-spray buffer and vegetated filter strip (uses on tomato and strawberries) are needed for mitigating the risk to aquatic organisms (see Section 5).

## 10. Concerns

### 10.1. 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<sup>18</sup> 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 need for further tests and risk assessment to unique human metabolites could not be finalised while an *in vitro* comparative metabolism study is not submitted (see Section 2).
- 2) Mepanipyrim was phototoxic in the *in vitro* study. The assessment of phototoxic and photomutagenic potential of mepanipyrim could not be finalised due to lack of methodology on addressing the *in vivo* potential as follow-up of positive *in vitro* results (see Section 2).
- 3) The consumer risk assessment could not be finalised considering the outstanding data to finalise the residue definitions for risk assessment in primary crops and in processed commodities and the required GAP compliant residue trial on protected tomatoes (see Section 3).
- 4) The consumer risk assessment from the consumption of water could not be finalised, while satisfactory information was not available to address the effect of water treatment processes on the nature of the residues that might be present in surface water, when surface water is abstracted for drinking water (see Section 4).

### 10.2. 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.

- 5) A high long-term risk was identified for wild mammals exposed to mepanipyrim via dietary exposure, for all the representative uses (see Section 5).
- 6) Mepanipyrim is considered to meet the criteria for endocrine disruptors for humans and wild mammals as non-target organisms for the EAS-modalities according to points 3.6.5 and 3.8.2 of Annex II of Regulation No 1107/2009, as amended by Commission Regulation (EU) 2018/605 (see Section 6).

<sup>18</sup> 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.

### 10.3. 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 9, has been evaluated as being effective, then 'risk identified' is not indicated in Table 5.)

In addition to the issues indicated below, mepanipyrim is considered to meet the criteria for endocrine disruption for humans and wild mammals as non-target organisms according to points 3.6.5 and 3.8.2 of Annex II of Regulation No 1107/2009, as amended by Commission Regulation (EU) 2018/605 (see Sections 6 and 10.2).

**Table 5:** Overview of concerns

Representative use		Vines (low volume application)	Vines (high volume application)	Strawberry (open field)	Strawberry (protected crop)	Tomato (open field)	Tomato (protected crop)
<b>Operator risk</b>	Risk identified		X		X		X
	Assessment not finalised						
<b>Worker risk</b>	Risk identified	X	X				
	Assessment not finalised						
<b>Resident/ bystander risk</b>	Risk identified						
	Assessment not finalised						
<b>Consumer risk</b>	Risk identified						
	Assessment not finalised	X <sup>3,4</sup>	X <sup>3,4</sup>	X <sup>3,4</sup>	X <sup>3,4</sup>	X <sup>3,4</sup>	X <sup>3,4</sup>
<b>Risk to wild non-target terrestrial vertebrates</b>	Risk identified	X <sup>5</sup>	X <sup>5</sup>	X <sup>5</sup>	X <sup>5</sup>	X <sup>5</sup>	X <sup>5</sup>
	Assessment not finalised						
<b>Risk to wild non-target terrestrial organisms other than vertebrates</b>	Risk identified						
	Assessment not finalised						
<b>Risk to aquatic organisms</b>	Risk identified						
	Assessment not finalised						

Representative use		Vines (low volume application)	Vines (high volume application)	Strawberry (open field)	Strawberry (protected crop)	Tomato (open field)	Tomato (protected crop)
<b>Groundwater exposure to active substance</b>	Legal parametric value breached						
	Assessment not finalised						
<b>Groundwater exposure to metabolites</b>	Legal parametric value breached						
	Parametric value of 10 µg/L <sup>(a)</sup> breached						
	Assessment not finalised						

The superscript numbers relate to the numbered points indicated in Sections 10.1 and 10.2. 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).

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## Abbreviations

AAOEL	acute acceptable operator exposure level
ADI	acceptable daily intake
AMA	Amphibian Metamorphosis Assay
AOEL	acceptable operator exposure level
AP	alkaline phosphatase
AR	applied radioactivity
ARfD	acute reference dose
Bw	body weight
CA	Chromosomal Aberration
CAS	Chemical Abstracts Service
CHO	Chinese hamster ovary
CI	confidence interval
CL	confidence limits
CLP	Classification, Labelling and Packaging
DT <sub>50</sub>	period required for 50% dissipation (define method of estimation)
DT <sub>90</sub>	period required for 90% dissipation (define method of estimation)
dw	dry weight
ECHA	European Chemicals Agency
ED	Endocrine Disruption/Endocrine Disruptor
EEC	European Economic Community
ETR	exposure toxicity ratio
FAO	Food and Agriculture Organization of the United Nations
FOCUS	Forum for the Co-ordination of Pesticide Fate Models and their Use
FSTRA	Fish Short-Term reproductive Assay
GAP	Good Agricultural Practice
GC	gas chromatography
HPLC	high-pressure liquid chromatography or high-performance liquid chromatography
HPLC–MS	high-pressure liquid chromatography–mass spectrometry
IESTI	international estimated short-term intake
ISO	International Organization for Standardization
iv	intravenous
LC	liquid chromatography
LC <sub>50</sub>	lethal concentration, median

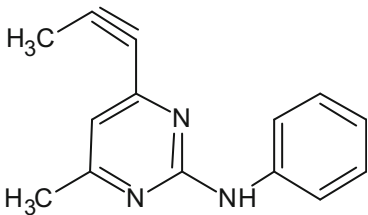
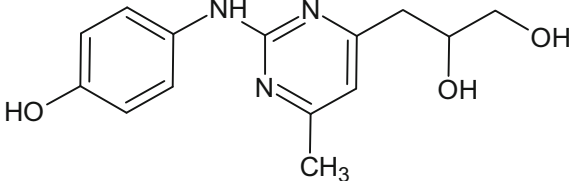
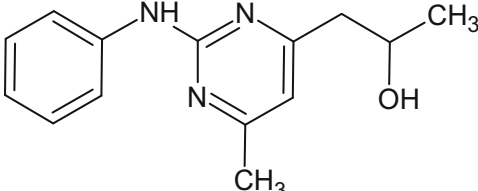
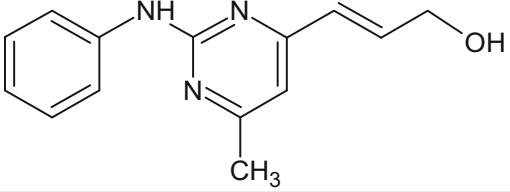
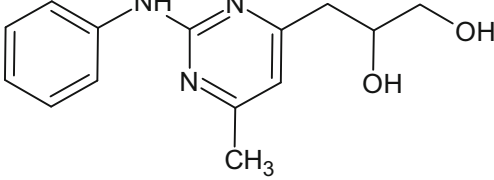
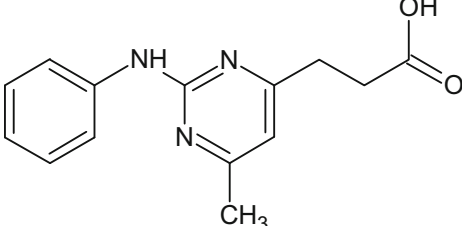
LC-MS	liquid chromatography–mass spectrometry
LC-MS-MS	liquid chromatography with tandem mass spectrometry
LOAEL	lowest observable adverse effect level
LOD	limit of detection
LOQ	limit of quantification
MCH	mean corpuscular haemoglobin
MCHC	mean corpuscular haemoglobin concentration
mm	millimetre (also used for mean measured concentrations)
mN	milli-Newton
MN	Micronucleus
MRL	maximum residue level
MS	mass spectrometry
MSDS	material safety data sheet
NOAEL	no observed adverse effect level
OECD	Organisation for Economic Co-operation and Development
PEC	predicted environmental concentration
PEC <sub>air</sub>	predicted environmental concentration in air
PEC <sub>gw</sub>	predicted environmental concentration in groundwater
PEC <sub>sed</sub>	predicted environmental concentration in sediment
PEC <sub>soil</sub>	predicted environmental concentration in soil
PEC <sub>sw</sub>	predicted environmental concentration in surface water
PHI	preharvest interval
PPE	personal protective equipment
PPR	Pesticides Peer Review
QSAR	quantitative structure–activity relationship
RUD	residue per unit dose
SFO	single first-order
SMILES	simplified molecular-input line-entry system
STMR	supervised trials median residue
t <sub>1/2</sub>	half-life (define method of estimation)
TRR	total radioactive residue
UF	uncertainty factor
UV	ultraviolet
W/S	water/sediment
w/v	weight per unit volume
w/w	weight per unit weight
WBC	white blood cell
WG	water-dispersible granule
WHO	World Health Organization
WP-SB	wettable powder in sealed water soluble bag



## **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.2023.8196>

## Appendix B – Used compound codes

Code/trivial name <sup>(a)</sup>	Chemical name/SMILES notation InChiKey <sup>(b)</sup>	Structural formula <sup>(b)</sup>
<b>mepanipyrim</b>	<i>N</i> -[4-methyl-6-(prop-1-ynyl)pyrimidin-2-yl]aniline <chem>Cc1cc(nc(Nc2ccccc2)n1)C#CC</chem> CIFWZNRJIBNXRE-UHFFFAOYSA-N	
<b>M11</b>	3-[2-(4-hydroxyanilino)-6-methyl-4-pyrimidinyl]-1,2-propanediol <chem>OCC(O)Cc2cc(C)nc(Nc1ccc(O)cc1)n2</chem> ZZNKMAMJVBHISI-UHFFFAOYSA-N	
<b>M31</b>	1-(2-anilino-6-methyl-4-pyrimidinyl)-2-propanol <chem>CC(O)Cc2cc(C)nc(Nc1ccccc1)n2</chem> OMAYAFSHSPBTA-UHFFFAOYSA-N	
<b>M33</b>	(2 <i>E</i> )-3-(2-anilino-6-methyl-4-pyrimidinyl)-2-propen-1-ol <chem>OC\C=C\Cc2cc(C)nc(Nc1ccccc1)n2</chem> YDTGUMSCZSFBGT-VMPITWQZSA-N	
<b>M36</b>	3-(2-anilino-6-methyl-4-pyrimidinyl)-1,2-propanediol <chem>OCC(O)Cc2cc(C)nc(Nc1ccccc1)n2</chem> WKVZPDPQDCVLLR-UHFFFAOYSA-N	
<b>B-11</b>	3-(2-anilino-6-methyl-4-pyrimidinyl)propanoic acid <chem>O=C(O)CCc2cc(C)nc(Nc1ccccc1)n2</chem> KOYBUQMDWAAXTL-UHFFFAOYSA-N	

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

(b): ACD/Name 2021.1.3 ACD/Labs 2021.1.3 (File Version N15E41, Build 123232, 7 July 2021) ACD/ChemSketch 2021.1.3 ACD/Labs 2021.1.3 (File Version C25H41, Build 123835, 28 August 2021).