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CONCLUSION ON PESTICIDES PEER REVIEW

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Peer review of the pesticide risk assessment of the active substance mepiquat (evaluated variant mepiquat chloride)

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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, Finland, and co-rapporteur Member State, Estonia, for the pesticide active substance mepiquat (evaluated variant mepiquat chloride) are reported. The context of the peer review was that required by Commission Implementing Regulation (EU) No 844/2012, as amended by Commission Implementing Regulation (EU) No 2018/1659. The conclusions were reached on the basis of the evaluation of the representative uses of mepiquat chloride as a plant growth regulator on cereals and grass (field uses). The reliable end points, appropriate for use in regulatory risk assessment, are presented. Missing information identified as being required by the regulatory framework is listed. Concerns are identified.

KEYWORDS

mepiquat, mepiquat chloride, peer review, pesticide, plant growth regulator, risk assessment

CONTENTS

SUMMARY

Commission Implementing Regulation (EU) No 844/2012, as amended by Commission Implementing Regulation (EU) No 2018/1659, 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 as amended by Commission Implementing Regulation (EU) No 2016/183. Mepiquat is one of the active substances listed in that Regulation.

In accordance with Article 1 of Regulation (EU) No 844/2012, the rapporteur Member State (RMS), Finland, and co-rapporteur Member State (co-RMS), Estonia, received an application from BASF SE for the renewal of approval of the active substance mepiquat chloride.

An initial evaluation of the dossier on mepiquat chloride was provided by the RMS in the renewal assessment report (RAR) and subsequently, a peer review of the pesticide risk assessment on the RMS evaluation was conducted by EFSA in accordance with Article 13 of Commission Implementing Regulation (EU) No 844/2012, as amended by Commission Implementing Regulation (EU) No 2018/1659. The following conclusions are derived.

The uses of mepiquat chloride according to the representative uses by field spraying for stem shortening (stabilisation) on cereals and grass (for seed production), as proposed at EU level, result in a sufficient plant growth regulatory efficacy.

The assessment of the data package revealed no issues that could not be finalised or that need to be included as critical areas of concern with respect to the **identity, physical, chemical and technical properties** of mepiquat chloride or the respective formulation, and **analytical methods**.

In the area of **mammalian toxicology** and non-dietary risk assessment, neither issues not finalised nor critical areas of concern were identified.

In the **residue** section, in view of the data gaps identified, the livestock exposure assessment and the consumer dietary risk assessment could not be finalised.

In the area of the **environmental fate and behaviour**, the information available was considered sufficient to complete the assessments necessary regarding the environmental exposure assessment at the EU level for the representative uses assessed, including confirmation that mepiquat chloride groundwater concentrations would be below the parametric drinking water limit of 0.1 µg/L. For the formulation for representative uses, this results in the identification of the potential for groundwater exposure by the second active substance ethephon above 0.1 µg/L when vulnerable shallow groundwater aquifers are overlain with neutral and alkaline soils, in two out of six FOCUS scenarios for the use assessed on grass and three out of nine FOCUS scenarios for the uses assessed on cereals.

In the section on **ecotoxicology**, neither issues not finalised nor critical areas of concern were identified.

According to 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, it can be concluded that mepiquat chloride is not an **endocrine disruptor**.

BACKGROUND

Commission Implementing Regulation (EU) No 844/2012,[1] as amended by Commission Implementing Regulation (EU) No 2018/1659[2] (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.[3] This regulates for the European Food Safety Authority (EFSA) the procedure for organising the consultation of Member States, the applicant(s) and the public on the initial evaluation provided by the rapporteur Member State (RMS) and/or co-rapporteur Member State (co-RMS) in the renewal assessment report (RAR), and the organisation of an expert consultation where appropriate.

In accordance with Article 13 of the Regulation, unless formally informed by the European Commission that a conclusion is not necessary, EFSA is required to adopt a conclusion on whether the active substance can be expected to meet the approval criteria provided for in Article 4 of Regulation (EC) No 1107/2009 within 5 months from the end of the period provided for the submission of written comments, subject to an extension of an additional 3 months where additional information is required to be submitted by the applicant(s) in accordance with Article 13(3). Furthermore, in accordance with Article 13(3a), where the information available in the dossier is not sufficient to conclude the assessment on whether the approval criteria for endocrine disruption are met, additional information can be requested to be submitted within a period of minimum 3 months, not exceeding 30 months, depending on the type of information requested.

In accordance with Article 1 of the Regulation, the RMS, Finland, and co-RMS, Estonia, received an application from BASF SE for the renewal of approval of the active substance mepiquat chloride. Complying with Article 8 of the Regulation, the RMS checked the completeness of the dossier and informed the applicant, the co-RMS (Estonia), the European Commission and EFSA about the admissibility.

The RMS provided its initial evaluation of the dossier on mepiquat chloride in the RAR, which was received by EFSA on 19 December 2018 (Finland, 2018).

In accordance with Article 12 of the Regulation, EFSA distributed the RAR to the Member States and the applicant BASF SE, for consultation and comments on 27 February 2019. 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 30 April 2019. At the same time, the collated comments were forwarded to the RMS for compilation and evaluation in the format of a reporting table. In addition, the applicant was invited to respond to the comments received. 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, the RMS and ECHA on 11 September 2019. 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.

In addition, following a consultation with Member States in the Pesticides Peer Review Experts' meetings PREV 25–26 (March 2020), it was considered necessary to apply an additional clock stop of 28 months in accordance with Commission Implementing Regulation (EU) No 2018/1659, to be able to conclude whether the approval criteria for endocrine disruption in line with the scientific criteria for the determination of endocrine disrupting properties, as laid down in Commission Regulation (EU) 2018/605,[4] are met.

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 May–June 2024.

This conclusion report summarises the outcome of the peer review of the risk assessment of the active substance and the formulation for representative uses, evaluated on the basis of the representative uses of mepiquat chloride as a plant growth regulator on cereals and grass (field uses), as proposed by the applicant. In accordance with Article 12(2) of Regulation (EC) No 1107/2009, risk mitigation options identified in the RAR and considered during the peer review, if any, are presented in the conclusion.

[1]Commission Implementing Regulation (EU) No 844/2012 of 18 September 2012 setting out the provisions necessary for the implementation of the renewal procedure for active substances, as provided for in Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market. OJ L 252, 19.9.2012, p. 26–32.

[2]Commission Implementing Regulation (EU) No 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.

[3]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.

[4]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.

A list of the relevant end points for the active substance and the formulation is provided in Appendix B. In addition, the considerations as regards the cut-off criteria for mepiquat chloride according to Annex II of Regulation (EC) No 1107/2009 are summarised in Appendix A.

A key supporting document to this conclusion is the peer review report (EFSA, 2024b), which is a compilation of the documentation developed to evaluate and address all issues raised in the peer review, from the initial commenting phase to the conclusion. The peer review report comprises the following documents, in which all views expressed during the course of the peer review, including minority views, where applicable, can be found:

- the comments received on the RAR;
- the reporting tables (17 September 2019 and 7 September 2023[5]);
- the evaluation table (14 June 2024);
- the reports of the scientific consultation with Member State experts (where relevant);
- the comments received on the assessment of the additional information (where relevant);
- the comments received on the draft EFSA conclusion.

Given the importance of the RAR, including its revisions (Finland, 2024), and the Peer Review Report, both documents are considered as background documents to this conclusion and thus are made publicly available.

It is recommended that this conclusion 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 FORMULATION FOR REPRESENTATIVE USES

Mepiquat is the ISO common name for 1,1-dimethylpiperidinium (IUPAC). Mepiquat chloride, a variant of mepiquat, is the modified ISO common name for 1,1-dimethylpiperidinium chloride.

The data submitted in the dossier refer to the variant mepiquat chloride.

The formulation for representative uses for the evaluation was 'BAS 098 00 W', a soluble concentrate (SL) containing 305 g/L mepiquat chloride and 155 g/L ethephon.[6]

The information on the active substances and the formulation for representative uses, including the co-formulant(s) in the formulation, was considered in the overall assessment during the peer review. None of the co-formulant(s) is an unacceptable co-formulant listed in Annex III of Regulation (EC) No 1107/2009.[7] Ethephon was considered as an active substance in accordance with Regulation (EC) No 1107/2009.[8] Details on the composition of the formulation cannot be reported in conclusions because of the provisions in Article 63(2)(d) of Regulation (EC) No 1107/2009; however, this information was fully available and evaluated during the peer review. A proposal for classification of the formulation according to Regulation (EC) 1272/2008 was provided by the applicant and assessed by the RMS (please see Volumes 3 CP of the RAR).

The representative uses evaluated comprise foliar spray applications for stem shortening (stabilisation) of barley, wheat and triticale in southern, central and northern Europe, on rye in central and northern Europe and on grass (for seed production) in northern Europe. Full details of the representative uses can be found in the list of end points in Appendix B.

Data were submitted to conclude that the representative uses of mepiquat chloride proposed at EU level result in sufficient plant growth regulatory efficacy on cereals and grass, following the guidance document SANCO/2012/11251-rev. 4 (European Commission, 2014b).

CONCLUSIONS OF THE EVALUATION

General Aspects

With regard to the mammalian toxicity information available for the formulation for representative uses 'BAS 098 00 W', studies were performed for acute toxicity endpoints. With regard to the co-formulant(s) contained in 'BAS 098 00 W', the experts considered that the available toxicological information sufficiently addressed the genotoxicity and repeated dose toxicity potential of 'BAS 098 00 W' over the short and long term. No concern was identified.[9]

[5]Reporting table following consultation on the revised RAR on the assessment of the endocrine-disrupting properties made available after the long-term ED clock stop.

[6]For the latter active substance (ethephon), the peer review of the renewal process was completed and an EFSA Conclusion was issued on 2 December 2022 (https://doi.org/10.2903/j.efsa.2023.7742) (EFSA, 2023).

[7]Commission Regulation (EU) 2021/383 of 3 March 2021 amending Annex III to Regulation (EC) No 1107/2009 of the European Parliament and Council listing co-formulants which are not accepted for inclusion in plant protection products. OJ L 74, 4.3.2021, p. 7–26.

[8]It was approved. Commission Implementing Regulation (EU) 2023/2591 of 21 November 2023 renewing the approval of the active substance ethephon in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council and amending Commission Implementing Regulation (EU) No 540/2011. OJ L, 2591, 22.11.2023, p. 1–5.

[9]See expert consultation point 2.16 in the Report of the Pesticides Peer Review Experts' TC 125 (January 2024) (EFSA, 2024b).

The availability of ecotoxicity data with the formulation for representative uses was discussed at the experts' meeting[10] (refer to Section 5). Furthermore, the experts also discussed the data retrieval search and the available data for the individual components. No concerns were identified.

1 | IDENTITY, PHYSICAL/CHEMICAL/TECHNICAL PROPERTIES AND METHODS OF ANALYSIS

The following guidance documents were followed in the production of this conclusion: European Commission (2000a, 2000b, 2010).

Mepiquat chloride is manufactured as a technical concentrate (TK) with the specification of the active substance content of 615–665 g/L, corresponding to a minimum purity of 990 g/kg on theoretical dry weight basis. The proposed specification is based on batches from industrial plant production. *N*-methylpiperidine is considered as a relevant impurity with a maximum level of 2 g/L in the technical concentrate (TK) and 3 g/kg on dry weight basis (see Section 2). Therefore, the current reference specification needs to be updated (in the current reference specification, *N*-methylpiperidine is included as a significant impurity at the same maximum levels). The batches used in the toxicological and ecotoxicological assessments support the current and the updated reference specification (see Sections 2 and 5). An FAO specification does not exist for mepiquat chloride.

The main data regarding the identity of mepiquat chloride and its physical and chemical properties are given in Appendix B.

Methods are available for the generation of data required for the risk assessment. Determination of mepiquat chloride in the active substance as manufactured can be done by high-pressure liquid chromatography with tandem mass spectrometry (HPLC–MS/MS). A CIPAC method is also available for the determination of mepiquat chloride in the technical material and adequate analytical methods based on the CIPAC method are available for the determination of the active substances mepiquat chloride and ethephon in the formulation for representative uses. A **data gap** for a method for the determination of the relevant impurity in the formulation was identified (see Section 10).

The residue definition for enforcement for food and feed of plant and animal origin was set as sum of mepiquat and its salts, expressed as mepiquat chloride. The limits of quantification (LOQs) of the monitoring methods are expressed as mepiquat chloride. Determination of the residues of mepiquat in food and feed of plant and animal origin can be done by HPLC-MS/MS methods with LOQs of 0.01 mg/kg in all commodities. HPLC-MS/MS method exists for monitoring the residues of mepiquat in soil with an LOQ of 0.01 mg/kg (expressed as mepiquat chloride). The determination of mepiquat in surface and drinking water is possible by HPLC-MS/MS method with an LOQ of 0.1 µg/L (expressed as mepiquat chloride). Residues of mepiquat in the air can be determined by ion chromatography with an LOQ of 0.0163 mg/m^3 (expressed as mepiquat chloride). The determination of mepiquat in body fluids is possible by HPLC-MS/MS with an LOQ of 0.05 mg/L (expressed as mepiquat chloride). Mepiquat in body tissues can be determined by using the monitoring method for residues in food of animal origin.

2 | MAMMALIAN TOXICITY

The following guidance documents were followed in the production of this conclusion: European Commission (2003, 2012), EFSA (2022), EFSA PPR Panel (2012) and ECHA (2017).

Mepiquat chloride was discussed at the Pesticides Peer Review Experts' Meeting PREV 25 (March 2020) and at the Pesticides Peer Review Experts' Teleconference (TC) 125 (January 2024).

N-methylpiperidine was identified as a toxicologically relevant impurity (being more acutely toxic than mepiquat chloride), but concluded to be of no concern at the proposed level in the current and newly proposed reference specification (maximum level of 2 g/L in TK and 3 g/kg on dry weight basis). Based on the available information, both the current and the proposed reference specifications are considered to be covered by toxicological testing.

Oral absorption of mepiquat chloride is rapid and accounts for 77% of the given dose. Mepiquat chloride distributes into organs and tissues, with the highest levels being reached in the liver, kidneys, urinary bladder and gastrointestinal tract, and it is then rapidly eliminated. When administered by the dermal route, the highest concentrations are found in blood cells or kidney. There is no evidence of accumulation of this active substance. After either oral or dermal exposure, the major excretion route for mepiquat chloride is through urine. Faecal elimination is limited, and pulmonary and biliary elimination are negligible.

In vivo, mepiquat chloride is not metabolised in the rat. In vitro, an interspecies comparative metabolism study (rat, mouse, dog and human) supports that there are no detectable metabolites of mepiquat chloride in any species, and no unique metabolites have been identified in humans.

[10]See expert consultation point 5.10 in the Report of the Pesticides Peer Review Experts' TC 129 (January–February 2024) (EFSA, 2024b).

Mepiquat chloride is classified (harmonised classification) as Acute Tox. 3; H301[11] and Acute Tox. 4; H332 via oral and inhalation routes, respectively, whereas it has low acute dermal toxicity. Mepiquat chloride is neither a skin irritant nor a skin sensitiser. It is not an eye irritant. According to Regulation (EU) No 283/2013,[12] the criteria for conducting a phototoxicity study and a photomutagenicity study are not met for mepiquat chloride.

Short-term dietary exposure to mepiquat chloride results in the dog in clinical signs (salivation) and vacuolisation of the kidney; in the rat in clinical signs including tremors, ataxia, impaired neurological function, increased crystals and nitrite in urine; whereas in the mouse, no clear evidence of systemic toxicity was observed. The relevant short-term oral no observed adverse effect level (NOAEL) is 58.4 mg/kg body weight (bw) per day from the 12-month dog study.

The weight of the evidence from the available in vitro and in vivo **genotoxicity** studies supports that mepiquat chloride is unlikely to be genotoxic in humans.

In a **long-term** dietary exposure study, the critical systemic effect in rats was a decrease in body weight and body weight gain. The relevant lowest observable adverse effect level (LOAEL) was 13 mg/kg bw per day (lowest tested dose in a 2-year carcinogenicity study). Due to the limited data available for mice, the long-term effects and respective NOAEL could not be identified for this species. Regarding carcinogenicity, in rats, there was an increase in the incidence of mammary gland fibroadenoma, thymoma and urothelial papilloma in males, and of uterine adenocarcinoma (with cervix) in females (NOAEL for rat carcinogenicity: 105 mg/kg bw per day). In the 2-year mouse study, no tumour was considered treatment-related.

With respect to **reproductive toxicity**, the parental NOAEL in a two-generation rat study was 52 mg/kg bw per day based on reduced maternal body weight during lactation of F2 pups. The same NOAEL of 155 mg/kg bw per day was established for both reproductive toxicity (shorter gestation time, lower number of litters, pups and liveborn pups), and offspring effects (reduced body weight gain and delayed development).

The most critical **developmental toxicity** effect of mepiquat chloride was the increased incidence of hydrocephaly observed in rabbit offspring, with a LOAEL of 50 mg/kg bw per day (lowest dose tested). Nevertheless, uncertainty was expressed as to whether this effect was treatment-related, in the absence of a dose–response relationship when taking the litter as a statistical unit and considering that the incidence was within that seen in historical control data. In the same study, the maternal NOAEL was 50 mg/kg bw per day for reduced food consumption and body weight gain. Signs of maternal and developmental toxicity of mepiquat chloride were also detected in rats at (slightly) higher doses (maternal NOAEL: 150 mg/kg bw per day; developmental NOAEL: 50 mg/kg bw per day).

The NOAEL in a rat acute **neurotoxicity** study was 174 mg/kg bw per day, based on findings on functional observational battery and decreased rearing and motor activity in males and females at the dose of 697 mg/kg bw per day. As already concluded in 2008 (EFSA, 2008a), the experts still support that some mepiquat-induced clinical signs such as tremors, ataxia, lack of motor coordination, decreased motor activity and abnormal posture are consistent with nicotinic receptors activation, whereas others, like bradypnea and salivation, may be due to muscarinic receptors activation. In a subchronic neurotoxicity study in rats, the NOAEL was 65.6 mg/kg bw per day, based on reduced body weight gain in females. The available developmental neurotoxicity (DNT) study in rats was considered acceptable by the experts.[13] The NOAEL for developmental neurotoxicity was 30 mg/kg bw per day based on a statistically significant decrease in the thickness of the corpus callosum both in male and female pups at PND 22 and PND 62 and when sexes are combined, at the top dose of 60 mg/kg bw per day, in the absence of maternal toxicity.[14]

As regards the **toxicological reference values** (TRVs),[15] the acceptable daily intake (**ADI**)[16] for mepiquat chloride has been set at 0.065 mg/kg bw per day based on the LOAEL of 13 mg/kg bw per day for decreased body weight and body weight gain in the 2-year rat study and an uncertainty factor (UF) of 200 (the standard UF 100 to cover for inter- and intra-species differences and an extra-factor of 2 to account for the extrapolation of the NOAEL from the LOAEL). The NOAEL of 30 mg/kg bw per day for pups' lethality observed at the top dose quite early in the DNT study (postnatal days (PND) 11–21) has been considered appropriate as a point of departure for the derivation of the acute reference dose (**ARfD**: 0.3 mg/kg bw, using an UF of 100), the acceptable operator exposure level (**AOEL**: 0.23 mg/kg bw per day, using an UF of 100 and correcting for 77% oral absorption) and the acute AOEL (**AAOEL:** 0.23 mg/kg bw, using an UF of 100 and correcting for 77% oral absorption).

Non-dietary exposure for operators, workers, bystanders and residents was estimated using the EFSA calculator (EFSA, 2022) and considering the agreed dermal absorption values of 0.32% for the formulation concentrate and 0.52% for the in-use dilution. As the representative product 'BAS 098 00 W' contains a second active substance (ethephon[17]), both individual and combined dermal exposures to these two active substances were considered for risk assessment.

[11]Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006. OJ L 353, 31.12.2008, p. 1–1355.

[12]Commission Regulation (EU) No 283/2013 of 1 March 2013 setting out the data requirements for active substances, in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market. *OJ L 93, 3.4.2013, p. 1–84*.

[13]See expert consultation point 2.13 in the Report of the Pesticides Peer Review Experts' Meeting TC 124 and TC 125 (January 2024) (EFSA, 2024b).

[14]See experts' consultation point 2.14 in the Report of the Pesticides Peer Review Experts' Meeting TC 124 and TC 125 (January 2024) (EFSA, 2024b).

[15]The reference values set in 2008 for mepiquat chloride (see EFSA, 2008a) were: for ADI, 0.2 mg/kg bw per day, based on the NOAEL of 19.9 mg/kg bw per day from the 12-month dietary study in dogs; for ARfD, 0.3 mg/kg bw, based on the NOAEL of 30 mg/kg bw per day obtained in the developmental neurotoxicity study; for AOEL, 0.3 mg/kg bw per day based on the NOAEL of 30.5 mg/kg bw per day from the 90-day study in dogs.

[16]See experts' consultation point 2.14 in the Report of the Pesticides Peer Review Experts' Meeting TC 124 and TC 125 (January 2024) (EFSA, 2024b).

[17]For ethephon, the dermal absorption values are 5.1% and 8.3% for the formulation concentrate and the in-use dilution, respectively.

For **operators,** even if not wearing gloves (PPE) during mixing, loading and application, the long-term and acute exposures to mepiquat chloride (alone) were estimated to be below the AOEL and AAOEL, respectively, for all representative uses. The combined short-term and acute operator exposure to mepiquat chloride and ethephon[18] is below the (A)AOEL if workwear and gloves during mixing and loading are used.

The exposure of **workers, bystanders and residents** to mepiquat chloride was estimated to be below the AOEL for the representative uses. The combined exposure to mepiquat chloride and ethephon (i.e. the sum of the percentages of their respective (A)AOELs) does not exceed 100% for any of the exposed groups.

The **metabolites** of mepiquat chloride found in animals and/or plants and requiring further toxicological considerations include 4-hydroxy mepiquat chloride, for which genotoxicity and general toxicity are considered to be covered by the reference values of the parent compound.[19]

3 | RESIDUES

The assessment in the residue section is based on the following guidance documents: OECD (2009, 2011), European Commission (2011) and JMPR (2004, 2007).

Mepiquat chloride was discussed at the Pesticides Peer Review Experts' Meeting PREV 27 in March 2020.

The metabolism of mepiquat chloride was investigated in fruit crops (grapes), in cereals (wheat, barley) and in pulses and oilseeds (cotton, oilseed rape) following foliar treatment using the ^{14}C-labelling form of the parent molecule. Mepiquat chloride was found to be the predominant compound of the total radioactive residues (TRR) in all crop parts (71% TRR in wheat grain to 99% TRR in rapeseed pods). The submitted metabolism studies were concluded to be acceptable and the overall metabolic pattern of mepiquat chloride was considered as sufficiently investigated in all crop parts. Although not triggered considering the DT_{90} for mepiquat chloride < 100 days, the metabolism of mepiquat chloride was investigated in rotational crops (wheat, radishes and lettuces) at the standard plant back intervals (PBIs) following bare soil application of ^{14}C-labelled mepiquat chloride (0.9N). At the different PBIs, a significant uptake of residues from the soil to the different plant parts of wheat and radishes was observed, while in lettuce, the total radioactive residues were very low (< 0.01–0.011 mg/kg). Mepiquat chloride was identified at very low concentrations in all crops (< 0.01 mg/kg) and the remaining extractable radioactivity was sufficiently characterised. Overall, a similar metabolic pattern as in primary crops could be observed in rotational crops. Mepiquat chloride remained stable under the standard hydrolysis conditions representative of pasteurisation, baking/brewing/boiling and sterilisation. On the basis of all these studies, the **residue definitions** for **enforcement** and **risk assessment** have been proposed as 'sum of mepiquat and its salts, expressed as mepiquat chloride'. They are applicable to all categories of primary crops following foliar application, for rotational crops and processed commodities.

Two and four acceptable good agricultural practice (GAP)-compliant residue trials were submitted, respectively, on barley and wheat from northern Europe (NEU) zone locations for the determination of mepiquat chloride residues. Six and four additional GAP-compliant residue trials, respectively, on barley and wheat are therefore required to complete the residue data set for this zone (**data gap,** see Section 9.1). Sufficient residue trials on wheat and barley and compliant with the respective southern Europe (SEU) GAP are available. All the available residue trials are supported by acceptable storage stability data and validated analytical methods. Sufficient GAP-compliant residues trials on grass were not available and are required (**data gap**, see Section 10).

In the metabolism studies conducted in poultry and ruminants with [2,6-^{14}C]-mepiquat chloride, the parent compound was found to be predominant in all animal tissues and in egg. In milk, the parent compound was recovered at a lower proportion (up to 44% TRR), while 4-hydroxy mepiquat chloride was found at significant levels in milk (24% TRR) and in liver (ca. 40% TRR), mainly under its conjugated form. The potential presence of this metabolite was not investigated in poultry tissues. The studies can be considered as valid even though the total residues in milk and eggs did not reach a plateau level, but the formation of additional pertinent compounds is not expected. For animal commodities, the **residue definition for enforcement** is set as 'sum of mepiquat and its salts expressed as mepiquat chloride'. For **risk assessment, the residue definition** is proposed as 'sum of mepiquat and 4-hydroxy mepiquat chloride (free and conjugated) and their salts expressed as mepiquat chloride'.

Feeding studies were triggered and were provided for poultry and ruminants. However, and since only the residue levels of mepiquat chloride were determined in all matrices, conversion factors for enforcement to risk assessment were derived on a provisional basis for milk and liver from the ruminant metabolism studies. The livestock dietary burden calculation could not be finalised in view of the identified data gaps for additional residue trials on wheat, barley and grass, and therefore, MRLs for products of animal origin can only be derived provisionally. A data gap is set for a ruminant feeding study analysing the residues in accordance with the agreed enforcement and risk assessment residue definitions and supported by acceptable storage stability data for mepiquat chloride and for 4-hydroxy mepiquat chloride, and by validated analytical methods (**data gap,** see Section 9.1). The need for the submission of a new poultry feeding study will be reconsidered pending upon the finalisation of the livestock dietary burden calculation and whether from the metabolism studies residues at levels above 0.01 mg/kg are expected in tissues and eggs.

[18]For ethephon, the newly established AOEL is 0.02 mg/kg bw per day and AAOEL is 0.05 mg/kg bw (EFSA, 2023).

[19]See experts' consultation point 2.11 in the Report of the Pesticide Peer Review Experts' Meeting 25 (March 2020) (EFSA, 2024b).

In view of the identified data gaps to propose robust MRLs for the representative uses and to finalise the livestock exposure assessment, a provisional dietary intake calculation has been carried out considering the risk assessment input values for mepiquat chloride for the representative uses on cereals and products of animal origin according to the EFSA PRIMo rev. 3.1 model. Chronic and acute dietary intake concerns were not identified (international estimated daily intake (IEDI): 19% of the ADI (NL toddler) and international estimated short-term intake (IESTI): 5% of the ARfD (wheat)). According to EFSA PRIMo rev. 2A model, the calculated IEDI accounted for 15% of the ADI (DK child) whilst the highest acute intake was 12% of the ARfD (wheat flour).

The residue definitions for enforcement and risk assessment for products of plant and animal origin have not been changed compared to those agreed under the review of the existing maximum residue levels (MRLs) for mepiquat chloride (EFSA, 2015). However, in the meantime, new MRLs were proposed (EFSA, 2018; EFSA, 2018; EFSA, 2018) and the presence of mepiquat chloride was reported in cultivated fungi due to carry over from cereal straw that has been treated in accordance with the representative uses and which is used as a substrate to cultivate mushrooms (see EFSA, 2019, 2024a and the experts' consultation[20]). Therefore, a brief screening assessment considering the uses reported in the Article 12 MRL review against the new ADI as proposed for mepiquat chloride (see Section 2) has been carried out. The outcome was that a chronic or acute risk for the consumers is unlikely (IEDI: 21% of the ADI (NL toddler) and IESTI: 17% of the ARfD (cultivated fungi)). It should be noted that this assessment is further affected by uncertainties such as the lack of metabolism data on fungi, specific consumption data for oyster mushrooms and residue trials to determine the accurate residue levels of mepiquat chloride in oyster mushrooms cultivated on treated wheat straw.

The formulation for representative uses contains a second active substance, ethephon, for which no residue data for the two proposed uses on cereals and on grass were reported in this RAR (Finland, 2024). For the use on cereals, a consumer risk assessment was performed in the context of the recent peer review of ethephon (EFSA, 2023) and resulted in a highest chronic exposure of 19% of the ADI (GEMS/Food G06) and a highest acute exposure of 14% of the ARfD (wheat) for ethephon when using revision 3.1 of the EFSA PRIMo. For this assessment, the use on cereals with the same or slightly more critical GAP conditions as in the current evaluation were considered. The formulation used was a soluble concentrate (SL) as proposed in the current assessment. For the representative use on grass, no information is available on potential residues in the current peer review on mepiquat and in the peer review on ethephon where the use on grass was not supported. Therefore, a data gap for sufficient number of GAP-compliant residues trials on grass was identified (**data gap**, see Section 10).

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, mepiquat chloride exhibited low to moderate persistence. Metabolites triggering identification and assessment were not formed. Mineralisation of [2,6-^{14}C] mepiquat chloride to carbon dioxide in aerobic soil incubations accounted for 43%–70% AR after 120 days. The formation of unextractable residues (not extracted by either acidified acetonitrile/water, ethyl acetate or acidified chloroform) for this radiolabel accounted for 16%–44% after 120–121 days. In an anaerobic soil incubation mepiquat chloride was essentially stable. It was also stable under the conditions of a laboratory soil photolysis study. Mepiquat chloride exhibited high to slight mobility in soil. It was concluded that the adsorption of mepiquat chloride is not pH dependent.

In laboratory incubations in dark aerobic natural sediment water systems, mepiquat chloride exhibited moderate persistence, partitioning to sediment (max 56% AR after 14 days). Metabolites triggering identification and assessment were not formed. The unextractable sediment fraction (not extracted by acetonitrile/water) was a sink for the [2,6-^{14}C] radiolabel, accounting for 27%–28% AR at study end (100 days). Mineralisation of this radiolabel was significant accounting for 62%–66% AR at the end of the study. Mepiquat chloride was stable in laboratory sterile aqueous photolysis investigations. The necessary surface water and sediment exposure assessments (predicted environmental concentrations (PEC) calculations) of mepiquat chloride were carried out using the FOCUS (FOCUS, 2001) step 1 and step 2 approach (version 3.2 of the Steps 1–2 in FOCUS calculator). Formulation PECsw were calculated for 'BAS 098 00 W' using the FOCUS SWASH spray drift calculator.

The necessary groundwater exposure assessments were appropriately carried out using FOCUS (European Commission, 2014a) scenarios and the models PEARL 4.4.4 and PELMO 5.5.3.[21] The potential for groundwater exposure from the representative uses by mepiquat chloride 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 provided appropriate information 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. At the point of abstraction of surface water to produce drinking water, concentrations of mepiquat chloride are expected to be low consequent to its partitioning to sediment and degrading in natural surface water. Any low level of mepiquat chloride residue present in the surface water would be expected to be stable during the disinfection processes of ozonation and chlorination based on the scientific literature presented, so would not form transformation products.

[20]See experts' consultation point 3.2 in the Report of the Pesticide Peer Review Experts' Meeting 27 (23–26 March 2020) (EFSA, 2024b).

[21]Simulations utilised the agreed Q10 of 2.58 (following EFSA, 2008b) and Walker equation coefficient of 0.7.

The PEC in soil, surface water, sediment and groundwater covering the representative uses assessed for mepiquat expressed as mepiquat chloride equivalents can be found in Appendix B. The PEC for ethephon and its metabolite covering the uses assessed except grass for seed, are available in the EFSA conclusion for ethephon (EFSA, 2023, with full details included in its Appendix B). Using the PEC for ethephon and its metabolite in the EFSA conclusion for ethephon (EFSA, 2023) for cereals as a surrogate for grass for seed was considered acceptable in this case, considering the commonality in phenology of cereals and grass grown for seed and the modelling of soil moisture resulting from similarity in foliage development and rooting depth expected between cereals and grass when grown for seed. Consequently, this means that using the formulation for representative uses, a high potential for groundwater exposure by the active substance ethephon when vulnerable shallow groundwater aquifers are overlain with neutral and alkaline soils has to be expected for two out of six FOCUS scenarios for the uses on grass and cereals considering the NEU GAP, and three out of nine FOCUS scenarios for the uses on cereals in the CEU and SEU GAP. A key to the persistence and mobility class wording used, relating these words to numerical DT and Koc endpoint values can be found in Appendix C.

5 | ECOTOXICOLOGY

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

The batches used in the ecotoxicity studies were compliant with the proposed and existing reference specifications.

Mepiquat chloride was discussed at the Pesticide Peer Review Experts' Meeting PREV 26 (March 2020), and at the Pesticides Peer Review Experts' Teleconference (TC) 129 (January–February 2024).

Suitable acute toxicity data for **birds** were available with both mepiquat chloride and the formulation for representative uses 'BAS 098 00 W'. The reliability of the only available study on reproduction with birds was discussed at the experts' meeting[22] because the exposure duration was only 6 weeks. Although this type of study is not commonly considered suitable, in the case of mepiquat chloride, the experts agreed to use it by considering the high margin of safety[23] in the risk assessment for the representative uses. However, as this study is not fully compliant with the data requested under Regulation (EU) No 283/2013 and leads to uncertainty, a new reproduction study with standard exposure duration may be needed in future risk assessments if a similar margin of safety is not observed. The acute risk assessment was performed with both the endpoint for mepiquat chloride and the formulation for representative uses 'BAS 098 00 W'. Based on the available assessment, low acute risk to birds was concluded for all the routes of exposure (dietary, secondary poisoning and exposure to contaminated water) for all the representative uses. A low long-term risk to birds from mepiquat chloride was indicated with the available risk assessment. A quantitative additive long-term risk assessment for birds considering the second active substance, ethephon, was not presented in the RAR. However, a calculation was provided by EFSA which demonstrated a low long-term risk for the combined assessment both for the use to cereals and grass for seed production.[24]

Suitable acute toxicity data for **mammals** were available with both mepiquat chloride and the formulation for representative uses 'BAS 098 00 W'. The long-term endpoint for **mammals** was discussed and agreed at the experts' meeting.[25] Based on the agreed acute and long-term endpoint, low dietary risk to cereals was concluded. For the representative uses in grass for seed production, high acute risk was identified at Tier 1. The acute risk was refined by considering a reduced deposition factor, specifically considering that the GAP is to grass for seed production at BBCH 31–39, and low risk was concluded. The need for an additive acute risk assessment for mammals was discussed at the experts' meeting where it was agreed that a quantitative calculation was not needed since mepiquat chloride drove the acute toxicity of the mixture.[26] A quantitative additive long-term risk assessment for mammals was not presented in the RAR; however, a calculation was provided by EFSA which indicated a low long-term risk for the combined assessment both for the use to cereals and grass for seed production.[27]

Suitable endpoints addressing the effect of mepiquat chloride to **aquatic organisms** were available for fish (acute and chronic), aquatic invertebrates (acute and chronic), algae and aquatic plants (*Lemna gibba* and *Myriophyllum spicatum)*. The formulation for representative uses 'BAS 098 00 W' contains two active substances, mepiquat chloride and ethephon. It was noted that for most of the provided studies with the formulation for representative uses only mepiquat chloride was measured. The validity of the available studies with the formulation was discussed in the experts' meeting. The experts agreed that these studies were not sufficiently reliable to derive an endpoint for the formulation because only one of the two active substances contained in the formulation (mepiquat chloride) was measured. The endpoint for the aquatic plant *Myriophyllum spicatum* was derived from a formulation study but expressed in terms of the active substance, assuming that all toxicity of the formulation is due to mepiquat chloride.[28] Based on the available assessment for mepiquat chloride, a low risk was concluded for all **aquatic organisms** using PECsw estimated with FOCUS step 1 following the use on cereals which were considered to cover all representative uses via the so-called 'risk envelope' approach. No relevant metabolites of mepiquat chloride

[22]See experts' consultation point 5.1 in the Report of the Pesticides Peer Review Experts' Meeting PREV 26 (23–25 March 2020) (EFSA, 2024b).

[23]With reproductive endpoint from the six-week exposure study for birds, the lowest long-term tier 1 TER = 46.1 compared to an assessment factor of 5.

[24]See experts' consultation point 5.10 in the Evaluation Table, section 5 (EFSA, 2024b).

[25]See experts' consultation point 5.9 in the Report of the Pesticides Peer Review Experts' TC 129 (January–February 2024) (EFSA, 2024b).

[26]See experts' consultation point 5.4 in the Report of the Pesticides Peer Review Experts' Meeting PREV 26 (23–25 March 2020) (EFSA, 2024b).

[27]See experts' consultation point 5.10 in the Evaluation Table, section 5 (EFSA, 2024b).

[28]See experts' consultation point 5.5 in the Report of the Pesticides Peer Review Experts' Meeting PREV 26 (23–25 March 2020) (EFSA, 2024b).

have been identified in aquatic test systems, and therefore, metabolites were not considered in the risk assessment. An additive long-term risk assessment considering the second active substance, ethephon, was not available. However, when considering the margin of safety obtained in the risk assessment for mepiquat chloride (low risk at FOCUS step 1) together with the margin of safety obtained for ethephon (low risk at FOCUS step 2) in EFSA (2023), it is clear that a low long-term risk would be indicated for the combined assessment both for the use to cereals and grass for seed production.

Acute and chronic toxicity tests on **honey bees** were available for mepiquat chloride and the formulation for representative uses. The honeybee larval endpoint was discussed and agreed at the experts' meeting.[29] The risk assessment was performed following the use on cereals which was considered to cover all representative uses via the 'risk envelope' approach. Based on the available data, low risk to **honey bees** for both mepiquat chloride and the formulation for representative uses, 'BAS 098 00 W', was concluded for all the different routes of exposure using both the European Commission (2002) and the EFSA (2013) guidance documents.

No assessment was available for sublethal effects (**data gap,** see Section 10). No assessment of the accumulative effects was available. No data were available to perform a risk assessment for bumble bees and solitary bees. Relevant plant metabolites were not identified; therefore, exposure to plant metabolites has not been considered further.

Tier 1 toxicity tests on **non-target arthropods** using the formulation for representative uses 'BAS 098 00 W' and mepiquat chloride were provided with the predatory mite *Typhlodromus pyri*. A tier 1 toxicity study with mepiquat chloride for *Aphidius rhopalosiphi* was available. Moreover, extended laboratory studies on *T. pyri* and the parasitic wasp *Aphidius rhopalosiphi* were submitted with the formulation for representative uses. Additionally, two tests carried out with *Chrysoperla carnea* and *Aleochara bilineata* were provided. Based on the available data, low in-field and off-field risk to non-target arthropods was concluded following the use on cereals which was considered to cover all the representative uses via the 'risk envelope' approach.

Chronic data with **earthworms** were available with the active substance and the formulation for representative uses 'BAS 98 00 W'. Based on the available data with the active substance, low risk was concluded for all the representative uses. The risk assessment showed low risk for cereals and grass for seed production scenarios. Data on **soil macro-organisms other than earthworms** were not available. However, considering the outcome of the risk assessment for non-target arthropods, the argumentation provided was accepted. Based on the available data, low risk was concluded to **soil micro-organisms**, **non-target terrestrial plants** and organisms involved in **biological methods for sewage treatment.**

6 | ENDOCRINE DISRUPTION PROPERTIES

The endocrine disruption properties of mepiquat chloride were discussed at the Pesticides Peer Review Joint Mammalian Toxicology-Ecotoxicology Experts' Teleconference (TC) 124 (January 2024).

To assess the endocrine disruption potential of mepiquat chloride **for humans** according to the ECHA/EFSA guidance (2018), the number and type of effects induced, and the magnitude and pattern of responses observed across studies were considered in order to determine whether mepiquat chloride interacts with the oestrogen, androgen and steroidogenesis (EAS) and thyroid (T)-mediated pathways. 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 analysis of the potential interaction of mepiquat chloride with the EAS- and T-signalling pathways using the available evidence in the data set.

With regard to the **T-modality**, T parameters were considered sufficiently investigated and a pattern of 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 ECHA/EFSA (2018) ED Guidance).

Regarding the **EAS-modalities**, EAS parameters were not sufficiently investigated, and no EAS-mediated adversity was observed in the available data set. Overall, the endocrine activity was considered sufficiently investigated and was negative. Therefore, it was concluded that the ED criteria are not met for the EAS-modalities (**Scenario 2a(ii)** of the ECHA/EFSA (2018) ED Guidance).

The outcome of the assessment reported above for humans also applies to **wild mammals as non-target organisms**.

For **non-mammalian species**, an Amphibian Metamorphosis Assay (AMA, OECD TG 231) and a Fish Short-Term Reproduction Assay (FSTRA, OECD TG 229) were available to sufficiently investigate the endocrine activity through the T- and EAS-modalities, respectively. Although limitations were noted in both studies,[30] a pattern of EATS-mediated endocrine activity was not identified.

Overall, it can be concluded that mepiquat chloride does not meet the ED criteria 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.[31]

[29]See experts' consultation point 5.6 in the Report of the Pesticides Peer Review Experts' Meeting PREV 26 (23–25 March 2020) (EFSA, 2024b).

[30]See experts' consultation points 5.7 and 5.8 in the Report of the Pesticides Peer Review Joint Mammalian toxicology-Ecotoxicology Experts' TC 124 related to the discussion for the EAS- and T- modalities for non-mammalian species, respectively (EFSA, 2024b).

[31]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.

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)	Ecotoxicology
Mepiquat chloride	Low risk to soil dwelling organisms

TABLE 2 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
Mepiquat chloride	No	Yes	–	–	Yes

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

TABLE 3 Surface water and sediment.

Compound (name and/or code)	Ecotoxicology
Mepiquat chloride	Low risk to aquatic organisms living in the surface water/sediment-dwelling organisms

TABLE 4 Air.

Compound (name and/or code)	Toxicology
Mepiquat chloride	Harmonised classification: Acute Tox. 4; H332 Rat LC_{50} inhalation ≥ 2.84 mg/L (head-nose) (test substance purity 58%)

8 | PARTICULAR CONDITIONS PROPOSED TO BE TAKEN INTO ACCOUNT BY RISK MANAGERS

Risk mitigation measures (RMMs) identified following consideration of Member State (MS) and/or applicant's proposal(s) during the peer review, if any, are presented in this section (Table 5). These measures applicable for human health and/or the environment leading to a reduction of exposure levels of operators, workers, bystanders/residents, environmental compartments and/or non-target organisms for the representative uses are listed below. The list may also cover any RMMs as appropriate, leading to an acceptable level of risks for the respective non-target organisms.

It is noted that final decisions on the need of RMMs to ensure the safe use of the plant protection product containing the concerned active substance will be taken by risk managers during the decision-making phase. Consideration of the validity and appropriateness of the RMMs remains the responsibility of MSs at product authorisation, taking into account their specific agricultural, plant health and environmental conditions at national level.

TABLE 5 Risk mitigation measures proposed for the representative uses assessed.

	Cereals	Wheat, triticale	Barley	Cereals	Grass
	CEU	SEU	SEU	NEU	NEU
Representative use	Spray	Spray	Spray	Spray	Spray
Operator risk	Use of PPE is required[a]	Use of PPE is required[a]	Use of PPE is required[a]	Use of PPE is required[a,b]	Use of PPE is required[a,b]
Worker exposure					
Bystander/resident exposure					

[a]For tractor-mounted applications: gloves during mixing and loading (EFSA, 2022) for co-exposure to mepiquat chloride and ethephon in the representative PPP.
[b]Exposure estimates for cereals and grass in NEU are covered by the other estimates in cereals as worst-case (CEU and SEU).

9 | CONCERNS AND RELATED DATA GAPS

9.1 | Issues that could not be finalised

An issue is listed as 'could not be finalised' if there is not enough information available to perform an assessment, even at the lowest tier level, for 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[32] 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:

1. The consumer dietary risk assessment could not be concluded since MRLs cannot be recommended for the representative uses on cereals (CEU GAPs on barley, wheat, triticale and rye) and considering that the livestock exposure assessment cannot be finalised (relevant for the CEU uses in cereals (barley, wheat, triticale, rye) and NEU uses on grass; see Section 3).

    a. Six and four additional GAP-compliant residue trials, respectively, on barley and wheat to complete the residue data sets for the NEU residues zone (relevant for the CEU uses in cereals, see Section 3).
    b. A ruminant feeding study analysing the residues in accordance with the agreed enforcement and risk assessment residue definitions and supported by acceptable storage stability data for mepiquat chloride and for 4-hydroxy mepiquat chloride, and by validated analytical methods (relevant for the uses in cereals and grass, see Section 3).

9.2 | Critical areas of concern

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

An issue is also listed as a critical area of concern if the assessment at a higher tier level could not be finalised due to 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:

Critical areas of concern were not identified.

9.3 | Overview of the concerns identified for each representative use considered (Table 6)

(If a particular condition proposed to be taken into account to manage an identified risk, as listed in Section 8, has been evaluated as being effective, then 'risk identified' is not indicated in Table 6.)

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

TABLE 6 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		Cereals (wheat, triticale, rye, barley)	Wheat, triticale	Barley	Cereals (wheat, triticale, rye, barley)	Grass
		CEU	SEU	SEU	NEU	NEU
Operator risk	Risk identified					
	Assessment not finalised					
Worker risk	Risk identified					
	Assessment not finalised					
Resident/bystander risk	Risk identified					
	Assessment not finalised					
Consumer risk	Risk identified					
	Assessment not finalised	X[1]	X[1]	X[1]	X[1]	X[1]
Risk to wild non-target terrestrial vertebrates	Risk identified					
	Assessment not finalised					
Risk to wild non-target terrestrial organisms other than vertebrates	Risk identified					
	Assessment not finalised					
Risk to aquatic organisms	Risk identified					
	Assessment not finalised					
Groundwater exposure to active substance	Legal parametric value breached	3/9 FOCUS scenarios[a]	3/9 FOCUS scenarios[a]	3/9 FOCUS scenarios[a]	2/6 FOCUS scenarios[a]	2/6 FOCUS scenarios[a]
	Assessment not finalised					
Groundwater exposure to metabolites	Legal parametric value breached[b]					
	Parametric value of 10 µg/L[c] breached					
	Assessment not finalised					

Note: The superscript numbers relate to the numbered points indicated in Section 9.1. Where there is no superscript number, see Section 4 for further information.

[a]Considering aquifers overlain with predominantly neutral and alkaline soils and the active substance ethephon (EFSA, 2023).

[b]When the consideration for classification made in the context of this evaluation under Regulation (EC) No 1107/2009 is confirmed under Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008.

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

10 | LIST OF OTHER OUTSTANDING ISSUES

Remaining data gaps not leading 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. Although not critical, these data gaps may lead to uncertainties in the assessment and are considered relevant.

These data gaps refer only to the representative uses assessed and are listed in the order of the sections:

- A method for determination of the relevant impurity in the formulation (relevant for all representative uses evaluated; see Section 1).
- Sufficient number of GAP-compliant residue trials with mepiquat and ethephon on grass (relevant for the use in grass, see Section 3).
- A study investigating sublethal effects to honeybees (relevant for all representative uses evaluated; see Section 5).

ABBREVIATIONS

AAOEL acute acceptable operator exposure level
ADI acceptable daily intake
AMA Amphibian Metamorphosis Assay
AOEL acceptable operator exposure level
ARfD acute reference dose
bw body weight
CI confidence interval
CIPAC Collaborative International Pesticides Analytical Council Limited
dw dry weight
EAS oestrogen, androgen and steroidogenesis modalities
FAO Food and Agriculture Organization of the United Nations
GAP Good Agricultural Practice
HPLC high-pressure liquid chromatography or high-performance liquid chromatography
HPLC–MS high-pressure liquid chromatography–mass spectrometry
IEDI international estimated daily intake
IESTI international estimated short-term intake
ISO International Organization for Standardization
IUPAC International Union of Pure and Applied Chemistry
iv Intravenous
JMPR Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues (Joint Meeting on Pesticide Residues)
LC liquid chromatography
LC_{50} lethal concentration, median
LOAEL lowest observable adverse effect level
LOQ limit of quantification
mm millimetre (also used for mean measured concentrations)
mN milli-Newton
MRL maximum residue level
MS mass spectrometry
NOAEL no observed adverse effect level
OECD Organisation for Economic Co-operation and Development
PPE personal protective equipment
QSAR quantitative structure–activity relationship
r^2 coefficient of determination
RAC regulatory acceptable concentration
RAR Renewal Assessment Report
WHO World Health Organization

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CONFLICT OF INTEREST

If you wish to access the declaration of interests of any expert contributing to an EFSA scientific assessment, please contact interestmanagement@efsa.europa.eu.

REQUESTOR

European Commission

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APPENDIX A

Consideration of cut-off criteria for mepiquat chloride according to Annex II of Regulation (EC) No 1107/2009 of the European Parliament and of the Council

Properties		Conclusion[a]
CMR	Carcinogenicity (C)	Mepiquat chloride is not considered to be carcinogenic according to point 3.6.3 of Annex II of Regulation (EC) 1107/2009
	Mutagenicity (M)	Mepiquat chloride is not considered to be a mutagen according to point 3.6.2 of Annex II of Regulation (EC) 1107/2009
	Toxic for Reproduction (R)	Mepiquat chloride is not considered to be toxic for reproduction according to point 3.6.4 of Annex II of Regulation (EC) 1107/2009
Endocrine disrupting properties		Mepiquat chloride is not considered to meet the criteria for endocrine disruption for humans and 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
POP	**Persistence** **Bioaccumulation** **Long-range transport**	Mepiquat chloride is not considered to be a persistent organic pollutant (POP) according to point 3.7.1 of Annex II of Regulation (EC) 1107/2009
PBT	**Persistence** **Bioaccumulation** **Toxicity**	Mepiquat chloride is not considered to be a persistent, bioaccumulative and toxic (PBT) substance according to point 3.7.2 of Annex II of Regulation (EC) 1107/2009
vPvB	**Persistence** **Bioaccumulation**	Mepiquat chloride is not considered to be a very persistent, very bioaccumulative substance according to point 3.7.3 of Annex II of Regulation (EC) 1107/2009

[a]see ECHA RAC Opinion 2021 (ECHA, 2021).

APPENDIX B

List of end points for the active substance and the formulation for representative uses

Appendix B can be found in the online version of this output ('Supporting information' section): https://doi.org/10.2903/j.efsa.2024.8923.

APPENDIX C

Wording EFSA used in section 4 of this conclusion, in relation to DT and Koc 'classes' exhibited by each compound assessed

Wording	DT_{50} normalised to 20°C for laboratory incubations[33] or not normalised DT_{50} for field studies (SFO equivalent, when biphasic, the DT_{90} was divided by 3.32 to estimate the DT50 when deciding on the wording to use)
Very low persistence	< 1 day
Low persistence	1–< 10 days
Moderate persistence	10–< 60 days
Medium persistence	60–< 100 days
High persistence	100 days to < 1 year
Very high persistence	A year or more

Note: These classes and descriptions are unrelated to any persistence class associated with the active substance cut-off criteria in Annex II of Regulation (EC) No 1107/2009. For consideration made in relation to Annex II, see Appendix A.

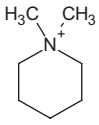
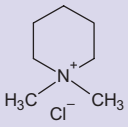
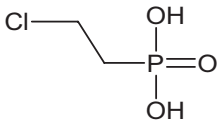
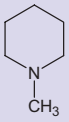
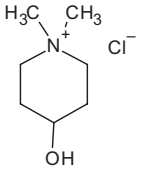
Wording	K_{oc} (either K_{Foc} or K_{doc}) mL/g
Very high mobility	0–50
High mobility	51–150
Medium mobility	151–500
Low mobility	501–2000
Slight mobility	2001–5000
Immobile	> 5000

Note: Based on McCall et al. (1980).

[33] For laboratory soil incubations, normalisation was also to field capacity soil moisture (pF2/10 kPa). For laboratory sediment water system incubations, the whole system DT values were used.

APPENDIX D

Used compound codes

Code/trivial name[a]	IUPAC name/SMILES notation/InChiKey[b]	Structural formula[c]
mepiquat	1,1-dimethylpiperidinium C[N+]1(C)CCCCC1 NNCAWEWCFVZOGF-UHFFFAOYSA-N	
mepiquat chloride	1,1-dimethylpiperidinium chloride [Cl-].C[N+]1(C)CCCCC1 VHOVSQVSAAQANU-UHFFFAOYSA-M	
ethephon	(2-chloroethyl)phosphonic acid ClCCP(=O)(O)O UDPGUMQDCGORJQ-UHFFFAOYSA-N	
***N*-methylpiperidine** (methyl piperidine)	1-methylpiperidine CN1CCCCC1 PAMIQIKDUOTOBW-UHFFFAOYSA-N	
4-hydroxy mepiquat chloride (4-OH-mepiquat chloride)	4-hydroxy-1,1-dimethylpiperidinium chloride [Cl-].C[N+]1(C)CCC(O)CC1 GDFMSGICPAHHIB-UHFFFAOYSA-M	
piperidine	piperidine C1CCCCN1 NQRYJNQNLNOLGT-UHFFFAOYSA-N	

[a]The metabolite name in bold is the name used in the conclusion.

[b]ACD/Name 2019.1.1 ACD/Labs 2019 Release (File version N05E41, Build 110555, 18 July 2019).

[c]ACD/ChemSketch 2019.1.1 ACD/Labs 2019 Release (File version C05H41, Build 110712, 24 July 2019).