Modification of the existing maximum residue levels for mepiquat in cotton seeds and animal commodities

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Abstract

In accordance with Article 6 of Regulation (EC) No 396/2005, the applicant, BASF SE, submitted an application to the competent national authority in Greece to modify the existing maximum residue level (MRL) for the active substance mepiquat in cotton seeds. The data submitted in support of the application were found to be sufficient to derive a MRL proposal for cotton seeds and the previously derived MRL proposals for animal commodities were found to be still valid. Adequate analytical methods for enforcement are available to control the residues of mepiquat chloride in the plant and animal commodities under consideration at the validated limit of quantification (LOQ) of 0.01 mg/kg. Based on the risk assessment results, EFSA concluded that the short-term and long-term intake of residues resulting from the use of mepiquat chloride according to the reported agricultural practices is unlikely to present a risk to consumer health.

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Summary

In accordance with Article 6 of Regulation (EC) No 396/2005, the applicant, BASF SE, submitted an application to the competent national authority in Greece (evaluating Member State (EMS)) to modify the existing maximum residue level (MRL) for the active substance mepiquat in cotton seeds. The EMS drafted an evaluation report in accordance with Article 8 of Regulation (EC) No 396/2005, which was submitted to the European Commission and forwarded to the European Food Safety Authority (EFSA) on 23 November 2016. In order to accommodate for the intended uses of mepiquat chloride, the EMS proposed to set an MRL for mepiquat in cotton seeds at 5 mg/kg. Concerning animal commodities, the EMS proposed to set MRLs for ruminant and equine liver at 0.6 mg/kg, for milk at 0.15 mg/kg and for eggs at 0.07 mg/kg.

EFSA assessed the application and the evaluation report as required by Article 10 of the MRL regulation. EFSA identified that the number of independent supervised residues trials was insufficient to derive an MRL for cotton seeds and identified points which needed further clarification, which were requested from the EMS. On 11 July 2018, the EMS submitted a revised evaluation report (which replaced the previously submitted evaluation report).

Based on the conclusions derived by EFSA in the framework of the EU pesticides peer review under Directive 91/414/EEC, the data evaluated under previous MRL assessments and the additional data provided by the EMS in the framework of the present MRL application, the following conclusions are derived.

The metabolism of mepiquat was investigated in three different crop groups as well as in rotational crops.

Studies investigating the effect of processing on the nature of mepiquat (hydrolysis studies) demonstrated that the active substance is stable under processing by pasteurisation, baking/brewing/boiling and sterilisation.

Based on the metabolic pattern of mepiquat chloride depicted in primary and rotational crops, the nature of the residues in processed commodities and the toxicological relevance of metabolites, the residue definitions for enforcement and risk assessment for plant products were proposed as the sum of mepiquat and its salts expressed as mepiquat chloride. EFSA concluded that for the current application the metabolism of mepiquat chloride is sufficiently addressed and the proposed residue definitions are applicable.

Sufficiently validated analytical methods based on liquid chromatography with tandem mass spectrometry (LC-MS/MS) are available to quantify residues in the crop assessed in this application according to the enforcement residue definition. The methods enable quantification of residues in high water-, high acid-, high oil- and dry/high starch- content commodities at or above 0.01 mg/kg (limit of quantification (LOQ)).

The available residue trials are sufficient to derive an MRL proposal of 6 mg/kg for cotton seeds for the intended use in southern EU Member States (southern Europe (SEU)).

Specific studies investigating the magnitude of mepiquat chloride residues in processed commodities were evaluated in the framework of the MRL review and subsequent EFSA reasoned opinions; and indicative processing factors have been derived for cotton delinted seeds, hulls, meal, crude oil and refined oil.

The occurrence of mepiquat residues in rotational crops was investigated in the framework of the EU pesticides peer review. Based on the available information on the nature and magnitude of residues, it was concluded that significant residue levels are unlikely to occur in rotational crops, provided that the active substance is used according to the proposed good agricultural practice (GAP).

As cotton seeds and their by-products are used as feed products, a potential carry-over of residues into food of animal origin was assessed. The nature of mepiquat residues in livestock has been investigated during the EU pesticides peer review and the residue definition for enforcement was proposed as the sum of mepiquat and its salts, expressed as mepiquat chloride; for risk assessment the residue was defined as the sum of mepiquat, 4-hydroxy-mepiquat and their salts, expressed as mepiquat chloride. The available metabolism studies allowed EFSA to derive a conversion factor of 1.7 from monitoring to risk assessment in ruminant liver. In all other animal matrices and since the parent mepiquat was the only significant compound of the total residues, a conversion factor of 1 was deemed to be sufficient.

The intended uses of mepiquat in cotton do not have a significant impact on the calculated livestock dietary burden and the assessment outcome is mainly driven by the existing uses. Thus, taking into account the contribution of cotton seeds and related by-products as well as feed items...
assessed in previous EFSA reasoned opinions, it is confirmed that the existing MRLs for certain animal commodities should be modified as suggested in the previous assessment of EFSA.

The toxicological profile of mepiquat was assessed in the framework of the EU pesticides peer review under Directive 91/414/EEC and the data were sufficient to derive an acceptable daily intake (ADI) of 0.2 mg/kg body weight (bw) per day and an acute reference dose (ARfD) of 0.3 mg/kg bw for mepiquat chloride. The metabolite 4-hydroxy-mepiquat chloride was concluded to be of comparable toxicity as the parent compound.

The consumer risk assessment was performed with revision 2 of the EFSA Pesticide Residues Intake Model (PRIMO). The highest long-term dietary intake accounted for 7.6% of the ADI (WHO cluster diet B). The contributions of mepiquat chloride residues in cotton seeds and in the animal commodities under consideration to the total estimated consumer exposure accounted for < 1% of the ADI.

No acute consumer risk was identified in relation to the MRLs proposed in the current assessment.

EFSA concluded that the proposed use of mepiquat chloride on cotton will not result in a consumer exposure exceeding the toxicological reference values and therefore is unlikely to pose a risk to consumers’ health.

EFSA proposes to amend the existing MRLs as reported in the summary table below.

Full details of all endpoints and the consumer risk assessment can be found in Appendices B-D.

| Code(a) | Commodity          | Existing EU MRL(b) / recently proposed amendment(c) (mg/kg) | Proposed EU MRL (mg/kg) | Comment/justification                                                                 |
|-------|--------------------|---------------------------------------------------------------|-------------------------|---------------------------------------------------------------------------------------|
| 0401090 | Cotton seeds       | sum of mepiquat and its salts, expressed as mepiquat chloride | 5(‡)/not relevant       | The submitted data are sufficient to derive an MRL proposal. Risk for consumers unlikely |
| 1011010 | Swine muscle       | 0.05*/0.05*                                                   | 0.05                    | MRL proposals based on livestock dietary intake calculation and available feeding studies when considering the contribution of the new intended uses in cotton and the contribution from the feed items assessed in previous EFSA reasoned opinions. Analytical methods for enforcement are available to control the residues of mepiquat chloride in animal commodities at the validated LOQ of 0.01 mg/kg Risk for consumers unlikely |
| 1011020 | Swine fat tissue   | 0.05*/0.05*                                                   | 0.05                    |                                                                                       |
| 1011030 | Swine liver        | 0.05*/0.07                                                    | 0.07                    |                                                                                       |
| 1011040 | Swine kidney       | 0.05*/0.07                                                    | 0.07                    |                                                                                       |
| 1012010 | Bovine muscle      | 0.09/0.06                                                    | 0.06                    |                                                                                       |
| 1012020 | Bovine fat tissue  | 0.06/0.05                                                    | 0.05                    |                                                                                       |
| 1012030 | Bovine liver       | 0.5/0.3                                                      | 0.3                     |                                                                                       |
| 1012040 | Bovine kidney      | 0.8/0.4                                                      | 0.4                     |                                                                                       |
| 1013010 | Sheep muscle       | 0.09/0.09                                                    | 0.09                    |                                                                                       |
| 1013020 | Sheep fat tissue   | 0.06/0.06                                                    | 0.06                    |                                                                                       |
| 1013030 | Sheep liver        | 0.5/0.6                                                      | 0.6                     |                                                                                       |
| 1013040 | Sheep kidney       | 0.8/0.7                                                      | 0.7                     |                                                                                       |
| 1014010 | Goat muscle        | 0.09/0.09                                                    | 0.09                    |                                                                                       |
| 1014020 | Goat fat tissue    | 0.06/0.06                                                    | 0.06                    |                                                                                       |
| 1014030 | Goat liver         | 0.5/0.6                                                      | 0.6                     |                                                                                       |
| 1014040 | Goat kidney        | 0.8/0.7                                                      | 0.7                     |                                                                                       |
| 1015010 | Equine muscle      | 0.09/0.06                                                    | 0.06                    |                                                                                       |
| 1015020 | Equine fat tissue  | 0.06/0.05                                                    | 0.05                    |                                                                                       |
| 1015030 | Equine liver       | 0.5/0.3                                                      | 0.3                     |                                                                                       |
| 1015040 | Equine kidney      | 0.8/0.4                                                      | 0.4                     |                                                                                       |
| 1016010 | Poultry muscle     | 0.05*/0.05*                                                   | 0.05                    |                                                                                       |
| 1016020 | Poultry fat tissue | 0.05*/0.05*                                                   | 0.05                    |                                                                                       |
| 1016030 | Poultry liver      | 0.05*/0.05*                                                   | 0.05                    |                                                                                       |
| 1020010 | Cattle milk        | 0.06/0.07                                                    | 0.07                    |                                                                                       |
| 1020020 | Sheep milk         | 0.06/0.15                                                    | 0.15                    |                                                                                       |
| 1020030 | Goat milk          | 0.06/0.15                                                    | 0.15                    |                                                                                       |

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### Modification of existing MRL for mepiquat in cotton seeds and animal commodities

| Code\(^{(a)}\) | Commodity      | Existing EU MRL\(^{(b)}/\text{recently proposed amendment}^{(c)}\) (mg/kg) | Proposed EU MRL (mg/kg) | Comment/justification |
|---------------|----------------|-------------------------------------------------------------------|-------------------------|------------------------|
| 1020040       | Horse milk     | 0.06/0.07                                                          | 0.07                    |                        |
| 1030000       | Birds eggs     | 0.05\(^{*}\)/0.07                                                 | 0.07                    |                        |

MRL: maximum residue level; LOQ: limit of quantification.

\(^{*}\): Indicates that the MRL is set at the limit of analytical quantification (LOQ).

\(^{(a)}\): Commodity code number according to Annex I of Regulation (EC) No 396/2005.

\(^{(b)}\): Existing EU MRL as amended by Commission Regulation (EU) No 2018/832.

\(^{(c)}\): MRL proposal derived in the reasoned opinion of EFSA on the modification of MRLs for various oilseeds and animal commodities issued in July 2018.

\(^{(ft)}\): MRL applicable until 30 June 2021, after that date 0.05 (*) mg/kg will be applicable unless modified by a Regulation.
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**Assessment**

The detailed description of the intended uses of mepiquat in cotton which are the basis for the current maximum residue level (MRL) application is reported in Appendix A.

Mepiquat is the ISO common name for 1,1-dimethylpiperidinium (IUPAC). In formulated products, usually, the variant mepiquat chloride is used as an active ingredient. The chemical structures of the active substance and its main metabolites are reported in Appendix E.

Mepiquat was evaluated in the framework of Directive 91/414/EEC1 with the United Kingdom designated as rapporteur Member State (RMS) where the representative use as a plant growth regulator in cereals for stem stabilisation was assessed. The draft assessment report (DAR) prepared by the RMS has been peer reviewed by the European Food Safety Authority (EFSA, 2008). Mepiquat was approved2 for the use as a plant growth regulator on 1 March 2009.

The EU MRLs for mepiquat are established in Annex II of Regulation (EC) No 396/20053 for the residue definition which comprises the sum of mepiquat and its salts, expressed as mepiquat chloride. The review of existing MRLs according to Article 12 of Regulation (EC) No 396/2005 (MRL review) has been performed (EFSA, 2015) and the proposed modifications have been implemented in the MRL legislation. In 2016, EFSA issued a reasoned opinion on the setting of a temporary MRL for cultivated fungi (EFSA, 2016).

Subsequent to the MRL review, Commission Regulation (EC) No 2016/10154 lowered the MRL for mepiquat in cotton seeds from the level of 5 mg/kg to the limit of quantification (LOQ) of 0.05* mg/kg, which was applicable from 19 January 2017. In order to accommodate an emergency authorisation for use of mepiquat chloride on cotton in Greece, a previous application was submitted to set a temporary MRL for mepiquat in cotton seeds. The competent national authority in Greece evaluated the application to set a temporary MRL and EFSA has assessed the application in a previous reasoned opinion (EFSA, 2018a), which has been implemented in the EU MRL regulations. Commission Regulation Reg. (EU) 2018/8325 set a temporary MRL for mepiquat in cotton seeds of 5 mg/kg applicable until 30 June 2021, after that date 0.05* mg/kg will be applicable unless modified by a Regulation.

A recent EFSA reasoned opinion on the modification of the existing MRL in various oilseeds and animal commodities (EFSA, 2018b) has not yet been considered and implemented in the EU MRL regulations.6

In accordance with Article 6 of Regulation (EC) No 396/2005, the applicant, BASF SE, submitted an application to the competent national authority in Greece (evaluating Member State (EMS)) to modify the existing MRLs for the active substance mepiquat in cotton seeds. The EMS drafted an evaluation report in accordance with Article 8 of Regulation (EC) No 396/2005, which was submitted to the European Commission and forwarded to the EFSA on 23 November 2016. EFSA assessed the application and the evaluation report as required by Article 10 of the Regulation. EFSA identified that the number of independent supervised residues trials was insufficient to derive an MRL for cotton seeds and identified points which needed further clarification, which were requested from the EMS. On 11 July 2018, the EMS submitted the requested information and provided a revised evaluation report (Greece, 2016), which replaced the previously submitted evaluation reports.

In order to accommodate for the intended uses of mepiquat chloride, the EMS proposed to set an MRL for mepiquat in cotton seeds at 5 mg/kg (Greece, 2016). Concerning animal commodities, the EMS proposed to set MRLs for ruminant and equine liver at 0.6 mg/kg, for milk at 0.15 mg/kg and for eggs at 0.07 mg/kg.

1 Council Directive 91/414/EEC of 15 July 1991 concerning the placing of plant protection products on the market. OJ L 230, 19.8.1991, p. 1–32.
2 Commission Decision 2008/108/EC of 26 November 2008 amending Council Directive 91/414/EEC to include flutolanil, benfluralin, fluzinam, fuberidazole and mepiquat as active substances. OJ L 317, 27.11.2008, p. 6–13.
3 Regulation (EC) No 396/2005 of the Parliament and of the Council of 23 February 2005 on maximum residue levels of pesticides in or on food and feed of plant and animal origin and amending Council Directive 91/414/EEC. OJ L 70, 16.3.2005, p. 1–16.
4 Commission Regulation (EU) 2016/1015 of 17 June 2016 amending Annexes II and III to Regulation (EC) No 396/2005 of the European Parliament and of the Council as regards maximum residue levels for 1-naphthylacetamide, 1-naphthylacetic acid, chloridazon, fluzinap-P, fuberidazole, mepiquat and tralkoxydim in or on certain products. OJ L 172/1, 29.6.2016, p. 1–21.
5 Commission Regulation (EU) 2018/832 of 5 June 2018 amending Annexes II, III and V to Regulation (EC) No 396/2005 of the European Parliament and of the Council as regards maximum residue levels for cyantaniliprole, cyanoxanil, deltamethrin, difenoconazole, fenamidone, flubendiamide, fluopicolide, folpet, fosetyl, mandestrobin, mepiquat, metazachlor, propamocarb, propargite, pyrimethanil, sulfadiazole and trifloxystrobin in or on certain products. OJ L 140/36, 6.6.2018, p. 38–86.
6 For an overview of all MRL Regulations on this active substance, please consult: http://ec.europa.eu/food/plant/pesticides/eu-pesticides-database/public/?event=pesticide.residue.selection&language=EN
EFSA based its assessment on the evaluation report submitted by the EMS (Greece, 2016), the draft assessment report (DAR) (and its addendum) (United Kingdom, 2005, 2008) prepared under Council Directive 91/414/EEC, the Commission review report on mepiquat (European Commission, 2008), the conclusion on the peer review of the pesticide risk assessment of the active substance mepiquat (EFSA, 2008), as well as the conclusions from EFSA opinions on the review of the existing MRLs for mepiquat according to Article 12 of Regulation (EC) No 396/2005 and recent MRL assessments (EFSA, 2015, 2016, 2018a,b).

For this application, the data requirements established in Regulation (EU) No 544/2011\(^7\) and the guidance documents applicable at the date of submission of the application to the EMS are applicable (European Commission, 1997a–g, 2000, 2010a,b, 2017; OECD, 2011, 2013). The assessment is performed in accordance with the legal provisions of the Uniform Principles for the Evaluation and the Authorisation of Plant Protection Products adopted by Commission Regulation (EU) No 546/2011\(^8\).

A selected list of end points of the studies assessed by EFSA in the framework of the this MRL application, including the end points of relevant studies assessed previously are presented in Appendix B.

The evaluation report submitted by the EMS (Greece, 2016) and the exposure calculations using the EFSA Pesticide Residues Intake Model (PRIMo) are considered as supporting documents to this reasoned opinion and, thus, are made publicly available as background documents to this reasoned opinion.

1. **Residues in plants**

1.1. **Nature of residues and methods of analysis in plants**

1.1.1. **Nature of residues in primary crops**

The nature of residues in primary crops resulting from the use of mepiquat chloride has been investigated in cereals (wheat, barley), pulses/oilseeds (cotton) and fruit (grapes) crops and assessed in the framework of the peer review (EFSA, 2008); and an additional study performed on rapeseed was assessed in the framework of the MRL review (EFSA, 2015). In all these studies, the only relevant component of the residues at harvest was mepiquat (72–90% of the total radioactive residue (TRR)). Some metabolites were present but they did not individually exceed 5% of the TRR and, therefore, were not further identified. The non-extractable radioactivity was low (≤ 6% TRR).

1.1.2. **Nature of residues in rotational crops**

Cotton can be grown in rotation with other plants and therefore the possible occurrence of residues in succeeding crops resulting from the use on primary crops has to be assessed. A confined rotational crop study using wheat, radish and lettuce planted in soil treated with mepiquat chloride was assessed during the peer review (EFSA, 2008). The experiments were performed with a higher application rate (9.3N) compared to the intended use for cotton seeds. Significant levels of total radioactivity were observed in the edible part of the rotational crops but no individual compound was identified at level at or above 0.05 mg/kg (EFSA, 2015). Mepiquat chloride was found to remain below the LOQ of 0.01 mg/kg. The remaining extractable radioactivity was associated to metabolites (free, conjugated or incorporated) resulting from the fragmentation of the ring. The non-extractable radioactivity was associated to fragments of the ring that had been incorporated into natural plant products. The metabolism in the rotational crops was found to be more extensive than in primary crops. However, as no relevant residues are expected in the succeeding crops, a specific residue definition for rotational crops was deemed as not necessary (EFSA, 2015). The good agricultural practices (GAPs) assessed in the MRL review were more critical than the new intended uses; therefore, this conclusion is still considered valid in the framework of the current application.

\(^7\) Commission Regulation (EU) No 544/2011 of 10 June 2011 implementing Regulation (EC) No 1107/2009 of the European Parliament and of the Council as regards the data requirements for active substances. OJ L 155, 11.6.2011, p. 1–66.

\(^8\) 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.
1.1.3. Nature of residues in processed commodities

The effect of processing on the nature of mepiquat residues was investigated in the framework of the peer review and it was demonstrated that mepiquat is stable under the standard hydrolysis conditions representative of pasteurisation, baking/brewing/boiling and sterilisation (EFSA, 2008).

1.1.4. Methods of analysis in plants

Sufficiently validated analytical methods are available for the determination of mepiquat residues in high water-, high acid-, high oil content and dry/starch matrices at a LOQ of 0.05 mg/kg (LOQ expressed as mepiquat chloride) (EFSA, 2008). A new analytical method by high-performance liquid chromatography with tandem mass spectrometry (HPLC–MS/MS) using a radiolabelled internal standard was provided and assessed with a previous MRL application (EFSA, 2018b). The new method is sufficiently validated for the determination of mepiquat residues in high water-, high acid-, high oil content and dry/starch commodities and allows for quantification of residues at the LOQ of 0.01 mg/kg (expressed as mepiquat chloride) (EFSA, 2018b).

1.1.5. Stability of residues in plants

Storage stability studies submitted with the current application (Greece, 2016) were evaluated during a previous EFSA assessment (EFSA, 2018a,b). Storage stability of mepiquat residues was demonstrated for a period of 24 months at −20°C in high water- (wheat forage) and high starch- (wheat grain) content commodities (EFSA, 2008) and for up to 25 months at −15°C in high oil- (cotton seeds) content commodities (EFSA, 2018a,b).

1.1.6. Proposed residue definitions

A general residue definition for both monitoring and risk assessment in all plant commodities can be proposed as the sum of mepiquat and its salts, expressed as mepiquat chloride (EFSA, 2008, 2015). This residue definition is also applicable to rotational crops and processed commodities.

1.2. Magnitude of residues in plants

1.2.1. Magnitude of residues in primary crops

The present application submitted five GAPs for the intended uses of mepiquat chloride as a plant growth regulator by spray application on cotton in SEU (Greece and Spain). Only the GAP for single application use (1 × 75 g a.s./ha at BBCH 50 – 69) is fully supported by the available residues trials. However, earlier applications are expected to have lower impact on the residue levels at harvest and therefore, due to the 14 day minimum interval between applications, it can reasonably be assumed that the GAP for single use application (1 × 75 g a.s.) at up to maximum growth stage BBCH 69 represents the critical GAP.

In support of the MRL application, the applicant submitted in total 12 GAP-compliant residue trials in cotton seeds conducted in Greece in the growing seasons of 2005, 2006 and 2017. The samples were analysed in accordance with the residue definitions for enforcement and risk assessment. According to the assessment of the EMS, the analytical methods used were sufficiently validated and fit for purpose. The samples of these residue trials were stored under conditions for which integrity of the samples have been demonstrated.

In the 2005 growing season, three trials were conducted with different crop varieties at the same location (Giannitsa), which were considered as different experimental conditions within the same trial (within the same experimental site). Where different experimental conditions exist within a same trial the highest residue value was used for MRL calculation (different experimental conditions). An additional trial was performed at a distinct location (Melissi). Although the two sites are in close geographical proximity, EFSA is of the opinion that the trials are sufficiently representative of the variability in agricultural practices and that the limited geographical independence of the two locations is a minor deviation considering that some trial parameters introduced variation.

Similarly in the 2006 season, three trials conducted with different crop varieties at the same location were considered as different experimental conditions within the same trial; the highest residue value was selected to calculate the MRL proposal. In addition, one valid trial performed at a different geographical location was available.
In the revised evaluation report, the EMS submitted data from four additional residue trials conducted in the 2017 growing season. The trials were conducted with different crop varieties at four distinct geographic locations in Thessaly (one trial) and Central Macedonia (three trials), Greece and were judged as sufficiently independent.

Overall, eight residue trials on cotton are sufficiently compliant with the critical GAP for cotton in SEU. A summary of residues data from the supervised residue trials is presented in Table B.1.2.1.

1.2.2. Magnitude of residues in rotational crops

Based on the available information on the magnitude of the residues, EFSA concluded that relevant residue levels are unlikely to occur in rotational crops provided that the compound is used according to proposed GAPs (see also Section 1.1.2).

1.2.3. Magnitude of residues in processed commodities

Studies investigating the magnitude of residues in processed commodities of rapeseed and cotton seeds were assessed in the framework of the peer review (EFSA, 2015, EFSA, 2018a) and during previous MRL assessments (EFSA, 2015). A processing study on cotton submitted with the current application (Greece, 2016) has been evaluated during a previous EFSA assessment. Based on the two processing residue trials, indicative processing factors for enforcement and risk assessment were derived in cotton delinted seeds, hulls, meal, crude oil and refined oil (EFSA, 2018a,b). The details are summarised in the Appendix B.

1.2.4. Proposed MRLs

The available data for the intended uses of mepiquat chloride on cotton in SEU are considered sufficient to derive an MRL proposal of 6 mg/kg for mepiquat in cotton seeds.

2. Residues in livestock

Cotton seeds and their by-products are used as feed products, and therefore, a potential carry-over of residues resulting from the use of mepiquat chloride into food of animal origin has to be assessed.

It is noted that in the framework of the MRL review (EFSA, 2015) the livestock dietary burden calculation was performed according to a different calculation methodology. In this reasoned opinion, the livestock dietary burden was calculated using the OECD methodology (OECD, 2013), taking into account the intended uses in cotton seed and the contribution of the intended uses in various other oilseeds evaluated during the previous EFSA assessment (EFSA, 2018b), as well as the contribution of other crops used for feed purpose for which an MRL has been implemented in the current legislation. The calculated dietary burdens exceeded the trigger value of 0.1 mg/kg dry matter (DM) for all livestock species.

2.1. Nature of residues and methods of analysis in livestock

The metabolism of mepiquat chloride has been investigated in lactating goats and laying hens and a general residue definition for monitoring was proposed as the sum of mepiquat and its salts, expressed as mepiquat chloride. For risk assessment, the residue definition was set as the sum of mepiquat, 4-hydroxy-mepiquat and their salts, expressed as mepiquat chloride (EFSA, 2008, 2015).

Methods of analysis for products of animal origin have been assessed by EFSA previously and were considered as sufficiently validated (EFSA 2015). Additional methods of analysis were provided with a previous MRL application and are considered as sufficiently validated (EFSA, 2018b). Storage stability of mepiquat was demonstrated for a period of 26 months at −18°C in all commodities of animal origin (EFSA, 2008).

2.2. Magnitude of residues in livestock

Feeding studies investigating the magnitude of mepiquat chloride residues in lactating goats and laying hens were reported in the framework of the peer review (EFSA, 2008). However, in the livestock feeding studies, samples were analysed for mepiquat only (expressed as mepiquat chloride). Therefore, based on the metabolism data, EFSA derived a conversion factor for monitoring to risk assessment of 1.7 in ruminant liver (EFSA, 2015). In all other animal matrices and since the parent mepiquat was the only significant compound of the total residues, a conversion factor of 1 was
deemed to be sufficient (EFSA, 2015). These values were used to derive MRL proposals and risk assessment values for animal commodities.

The dietary burden has been calculated considering the input values for cotton seeds/meal resulting from the current intended uses and the highest residue (HR)/supervised trials median residue (STMR) values for the feed items assessed in previous EFSA reasoned opinions (EFSA, 2015, 2018b). The assessment outcome is mainly driven by the existing uses while the intended uses of mepiquat chloride on cotton seeds do not have a significant impact on the estimated maximum livestock exposure. According to the results of these studies, MRL proposals for animal products have been derived which are summarised in Appendix B.4. The derived MRL proposals are in line with the recommended MRLs derived in the previous EFSA assessment (EFSA, 2018b).

3. Consumer risk assessment

The toxicological profile of mepiquat chloride was assessed in the framework of the peer review under Directive 91/414/EEC and the data were sufficient to derive an acceptable daily intake (ADI) of 0.2 mg/kg body weight (bw) per day and an acute reference dose (ARfD) of 0.3 mg/kg bw (EFSA, 2008). The metabolite 4-hydroxy-mepiquat chloride was concluded to be of comparable toxicity as the parent compound (EFSA, 2008). EFSA performed a dietary risk assessment using revision 2 of the EFSA PRIMo (EFSA, 2007). This exposure assessment model contains food consumption data for different subgroups of the EU population and allows the acute and chronic exposure assessment to be performed in accordance with the internationally agreed methodology for pesticide residues (FAO, 2016).

The long-term exposure was performed taking into account the STMR values derived for cotton seeds in this application. For the remaining commodities (including animal products), the STMR values from previous EFSA assessments were used as input values. The estimated long-term dietary intake of mepiquat chloride was in the range of 0–7.6% of the ADI (WHO cluster diet B). The contributions of mepiquat chloride residues in cotton seed and in the animal commodities under consideration to the total estimated consumer exposure accounted for <1% of the ADI.

The acute exposure assessment was performed only with regard to the commodities under consideration assuming the consumption of a large portion of the food items as reported in the national food surveys and that these items contained residues at the highest level as observed in supervised field trials (EFSA, 2007). However as cotton seeds are usually bulked, the STMR values were used for the acute risk assessment. The calculated maximum exposure in percentage of the ARfD accounted for 2.1% for bovine milk and milk products, 1.3% for bovine liver and <1% for other commodities. The contribution of residues in cotton seeds accounted for <0.01% of the ARfD.

The assessment outcome is driven by the existing uses while the intended uses of mepiquat chloride on cotton seeds do not have a significant impact on the consumer risk assessment. For further details on the exposure calculations, a screenshot of the report sheet of the PRIMo is presented in Appendix C.

4. Conclusion and Recommendations

The data submitted in support of this MRL application were found to be sufficient to derive an MRL proposal for cotton seeds. The livestock dietary burdens were reassessed according to the latest OECD methodology. The assessment outcome is driven by the existing uses while the intended uses of mepiquat chloride on cotton seeds do not have a significant impact on the estimated maximum livestock exposure. The MRLs proposed for products of animal origin are mainly resulting from the assessment with the new methodology. This is highlighted for risk manager consideration.

EFSA concluded that the proposed use of mepiquat on cotton seeds will not result in a consumer exposure exceeding the toxicological reference values and therefore is unlikely to pose a risk to consumers’ health.

The MRL recommendations are summarised in Appendix B.4.

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**Abbreviations**

- a.s. active substance
- ADI acceptable daily intake
- AR applied radioactivity
- ARfD acute reference dose
| Abbreviation | Description |
|--------------|-------------|
| BBCH         | growth stages of mono- and dicotyledonous plants |
| bw           | body weight |
| CF           | conversion factor for enforcement to risk assessment residue definition |
| CV           | coefficient of variation (relative standard deviation) |
| DAR          | draft assessment report |
| DAT          | days after treatment |
| DM           | dry matter |
| EMS          | evaluating Member State |
| FAO          | Food and Agriculture Organization of the United Nations |
| GAP          | Good Agricultural Practice |
| HPLC-MS/MS   | high performance liquid chromatography with tandem mass spectrometry |
| HR           | highest residue |
| IEDI         | international estimated daily intake |
| IESTI        | international estimated short-term intake |
| ILV          | independent laboratory validation |
| ISO          | International Organisation for Standardisation |
| IUPAC        | International Union of Pure and Applied Chemistry |
| LC           | liquid chromatography |
| LOQ          | limit of quantification |
| MRL          | maximum residue level |
| MS/MS        | tandem mass spectrometry detector |
| NEU          | northern Europe |
| OECD         | Organisation for Economic Co-operation and Development |
| PBI          | plant-back interval |
| PF           | processing factor |
| PHI          | preharvest interval |
| PRIMo        | (EFSA) Pesticide Residues Intake Model |
| RA           | risk assessment |
| RAC          | raw agricultural commodity |
| RD           | residue definition |
| RMS          | rapporteur Member State |
| SANCO        | Directorate-General for Health and Consumers |
| SEU          | southern Europe |
| SL           | soluble concentrate |
| STMR         | supervised trials median residue |
| TRR          | total radioactive residue |
| WHO          | World Health Organization |
### Appendix A – Summary of intended GAP triggering the amendment of existing EU MRLs

| Crop and/or situation | NEU, SEU, MS or country | F or I(a) | Pests or group of pests controlled | Preparation Type(b) | Conc. a.s. | Method kind | Range of growth stages and season(c) | Number min–max | Interval between application (min) | Application rate per treatment g a.s./ha min–max | Water L/ha min–max | Rate | Unit | PHI (days)(d) | Remarks |
|-----------------------|-------------------------|-----------|-----------------------------------|---------------------|-----------|------------|-------------------------------------|----------------|----------------------------------|-----------------------------------------------|-------------------|------|------|-----------|---------|
| Cotton seeds          | SEU (Greece)            | F         | Plant growth regulator            | SL 50 g/L           | Spray     | BBCH 50-69| 1                                          | –               | 400                               | 75 g a.s./ha                                                | –                 | Maximum total dose of 75 g mepiquat chloride/ha |
| Cotton seeds          | SEU (Greece)            | F         | Plant growth regulator            | SL 50 g/L           | Spray     | BBCH 50-69| 3                                          | 14              | 600                               | 25 g a.s./ha                                               | –                 | Maximum total dose of 75 g mepiquat chloride/ha |
| Cotton seeds          | SEU (Greece)            | F         | Plant growth regulator            | SL 50 g/L           | Spray     | BBCH 50-69| 6                                          | 14              | 600                               | 12.5 g a.s./ha                                            | –                 | Maximum total dose of 75 g mepiquat chloride/ha |
| Cotton seeds          | SEU (Spain)             | F         | Plant growth regulator            | SL 50 g/L           | Spray     | BBCH 60-67| 2                                          | 14              | 0.4–25                            | 200–600 1) 50 2) 25 g a.s./ha                             | –                 | Maximum total dose of 75 g mepiquat chloride/ha |
| Cotton seeds          | SEU (Spain)             | F         | Plant growth regulator            | SL 50 g/L           | Spray     | BBCH 60-67| 4                                          | 14              | 2–12.5                             | 200–600 1) 25 2) 12.5 3) 12.5 4) 12.5 g a.s./ha             | –                 | Maximum total dose of 75 g mepiquat chloride/ha |

MRL: maximum residue level; GAP: Good Agricultural Practice; NEU: northern European Union; SEU: southern European Union; MS: Member State; a.s.: active substance; SL: soluble concentrate.

(a): Outdoor or field use (F), greenhouse application (G) or indoor application (I).

(b): CropLife International Technical Monograph no 2, 6th Edition. Revised May 2008. Catalogue of pesticide formulation types and international coding system.

(c): Growth stage range from first to last treatment (BBCH Monograph, Growth Stages of Plants, 1997, Blackwell, ISBN 3-8263-3152-4), including, where relevant, information on season at time of application.

(d): PHI: minimum pre-harvest interval.
Appendix B – List of end points

B.1. Residues in plants

B.1.1. Nature of residues and methods of analysis in plants

B.1.1.1. Metabolism studies, methods of analysis and residue definitions in plants

| Crop groups               | Crop(s)   | Application(s)          | Sampling (DAT) | Comment/source                                      |
|---------------------------|-----------|-------------------------|----------------|-----------------------------------------------------|
| **Primary crops**         |           |                         |                |                                                     |
| Fruit crops               | Grapes    | Foliar, 2 × 1.1 kg a.s./ha | 98             | Ring-labelled 14C-mepiquat chloride (EFSA, 2008)    |
| Cereals/grass             | Wheat     | Foliar, 1 × 0.7 kg a.s./ha | 0, 8, 71       | Ring-labelled 14C-mepiquat chloride (EFSA, 2008)    |
|                           | Barley    | Foliar, 1 × 0.91 kg a.s./ha | 16, 37, 52     | Ring-labelled 14C-mepiquat chloride (EFSA, 2008)    |
| Pulses/oilseeds           | Cotton    | Foliar, 1 × 0.16 kg a.s./ha | 15, 67         | Ring-labelled 14C-mepiquat chloride (EFSA, 2008)    |
|                           | Rapeseed  | Foliar, 2 × 0.3 kg a.s./ha | 63             | Ring-labelled 14C-mepiquat chloride (EFSA, 2015)    |
| **Rotational crops**      |           |                         |                |                                                     |
| Root/tuber crops          | Radish    | Bare soil, 0.7 kg a.s./ha (9.3 N the intended use GAP for cotton seeds) | 29, 120, 365  | Ring-labelled 14C-mepiquat chloride (EFSA, 2008)    |
| Leafy crops               | Lettuce   |                         |                |                                                     |
| Cereals (small grain)     | Wheat     |                         | 29, 120, 365   |                                                     |
| Processed commodities     |           |                         |                |                                                     |
| (hydrolysis study)        | Conditions| Stable?                 | Comment/source  |                                                     |
| Pasteurisation (20 min, 90°C, pH 4) | Yes | EFSA (2018a,b)          |                |                                                     |
| Baking, brewing and boiling (60 min, 100°C, pH 5) | Yes |                           |                |                                                     |
| Sterilisation (20 min, 120°C, pH 6) | Yes |                           |                |                                                     |
Can a general residue definition be proposed for primary crops?
Yes EFSA (2008)

Rotational crop and primary crop metabolism similar?
Yes The metabolic pattern depicted in rotational crops was found to be more extensive than in primary crops. However, as no relevant residues are expected in the succeeding crops, a specific residue definition is not necessary for rotational crops (EFSA, 2015)

Residue pattern in processed commodities similar to residue pattern in raw commodities?
Yes EFSA (2008)

Plant residue definition for monitoring (RD-Mo)
Sum of mepiquat and its salts, expressed as mepiquat chloride

Plant residue definition for risk assessment (RD-RA)
Sum of mepiquat and its salts, expressed as mepiquat chloride

Methods of analysis for monitoring of residues (analytical technique, crop groups, LOQs)
Matrices with high water content, high oil content, high acid content and dry/high starch matrices:
HPLC–MS/MS, LOQ 0.05 mg/kg (EFSA, 2008; Greece, 2016)
HPLC-MS/MS, LOQ 0.01 mg/kg (expressed as mepiquat-chloride)(EFSA, 2018b)
Confirmatory methods available
ILVs available

DAT: days after treatment; a.s.: active substance; PBI: plant-back interval; HPLC-MS/MS: high-performance liquid chromatography with tandem mass spectrometry; LOQ: limit of quantification; ILV: independent laboratory validation.

### B.1.1.2. Stability of residues in plants

| Plant products (available studies) | Category | Commodity | T (°C) | Stability period Value | Compounds covered | Comment/Source |
|-----------------------------------|----------|-----------|--------|------------------------|-------------------|----------------|
| High water content                | Wheat forage | –20       | 24 Months | Mepiquat | EFSA (2018a,b) |
| Cotton forage                     | –15       | 25 Months | Mepiquat |                        | Greece (2016), EFSA (2018a) |
| High oil content                  | Cotton seeds, cotton seeds (delinted) | –15     | 25 Months | Mepiquat | Greece (2016), EFSA (2018a) |
| Dry/High starch                    | Wheat grain | –20       | 24 Months | Mepiquat | EFSA (2018a,b) |
### B.1.2. Magnitude of residues in plants

#### B.1.2.1. Summary of residues data from the supervised residue trials

| Commodity       | Region/indoor\(^{(a)}\) | Residue levels observed in the supervised residue trials (mg/kg) | Comments/source                                                                 | Calculated MRL (mg/kg) | HR\(^{(b)}\) (mg/kg) | STMR\(^{(c)}\) (mg/kg) |
|-----------------|--------------------------|-----------------------------------------------------------------|--------------------------------------------------------------------------------|------------------------|----------------------|------------------------|
| Cotton seeds    | SEU                      | 0.41, 0.87\(^{(d)}\), 1.13\(^{(d)}\), 1.62\(^{(d)}\), 1.89, 1.91\(^{(e)}\), 2.44\(^{(d)}\), 3.19\(^{(e)}\) | Residue trials on cotton compliant with the critical GAP (1 × 75 g a.s./ha at BBCH 50-69) | 6                      | 3.19                 | 1.76                   |

MRL: maximum residue level; GAP: Good Agricultural Practice; a.s.: active substance; BBCH: growth stages of mono- and dicotyledonous plants.

\(^{(a)}\): NEU: Outdoor trials conducted in northern Europe, SEU: Outdoor trials conducted in southern Europe, Indoor: indoor EU trials or Country code: if non-EU trials.

\(^{(b)}\): HR: Highest residue. The highest residue for risk assessment refers to the whole commodity and not to the edible portion.

\(^{(c)}\): STMR: Supervised trials median residue according to the residue definition for monitoring.

\(^{(d)}\): Trials conducted at a nominal water application rate per treatment (500 L/ha) at the limit of the 25% tolerance rule for the GAP for single application use (400 L/ha). The measured water application rate per treatment slightly exceeded the 25% tolerance rule in two trials (503 and 507 L/ha), however EFSA is of the opinion that exceedance of the water application rate is a minor deviation and that the trials could be considered as GAP compliant.

\(^{(e)}\): Trials performed at locations with limited geographical independence (Melissi and Giannitsa, Greece; 5.65 km straight line between municipal centres; trial location coordinates not reported).

Supported by evidence in the study reports indicating different soil types (clay loam or silty loam) and different preceding year crops (sugar beet or cotton) at the trial locations, EFSA is of the opinion that the geographical independence of the two locations is a minor deviation and that two trials could be accepted.
### B.1.2.2. Residues in rotational crops

Residues in rotational and succeeding crops expected based on confined rotational crop study?

| Processing factor (PF) | CF<sub>p</sub>(c) | Comment/source |
|------------------------|-------------------|----------------|
| Residues > 0.01 mg/kg not expected when mepiquat chloride is applied in accordance with the intended use on cotton seeds. | | Greece (2016), EFSA (2018a) |

Not triggered

### B.1.2.3. Processing factors

Processing studies submitted with the current application were evaluated during previous EFSA assessments (EFSA, 2018a, b).

| Processed commodity | Number of valid studies<sup>(a)</sup> | Processing factor (PF) | CF<sub>p</sub><sup>(c)</sup> | Comment/source |
|---------------------|--------------------------------------|------------------------|-------------------|----------------|
| Cotton delinted seeds | 2 | Individual values: 1.1; 1.4 | Mean PF<sup>(b)</sup>: 1.2 | 1.0 | Greece (2016), EFSA (2018a) |
| Cotton hulls | 2 | 0.2; 0.3 | 0.3 | 1.0 |
| Cotton meal | 2 | 1.7; 2.1 | 1.9 | 1.0 |
| Cotton crude oil | 2 | < 0.1; < 0.1 | < 0.1 | 1.0 |
| Cotton refined oil | 2 | < 0.1; < 0.1 | < 0.1 | 1.0 |

<sup>(a)</sup>: Studies with residues in the RAC at or close to the LOQ were disregarded (unless concentration may occur).

<sup>(b)</sup>: The median processing factor is obtained by calculating the median of the individual processing factors of each processing study.

<sup>(c)</sup>: Conversion factor for risk assessment in the processed commodity; median of the individual conversion factors for each processing residues trial.

### B.2. Residues in livestock

#### Relevant groups (subgroups)

| Relevant groups (subgroups) | Dietary burden expressed in mg/kg bw per day Median | Maximum | mg/kg DM Median | Maximum | Most critical subgroup<sup>(a)</sup> mg/kg bw | Most critical commodity<sup>(b)</sup> | Trigger exceeded (Y/N) max burden |
|----------------------------|------------------------|----------|-----------------|----------|-----------------------------|-----------------------------|-----------------|
| Cattle (all diets) | 0.381 | 0.571 | 12.09 | 17.05 | Cattle (dairy) | Rye, straw | Yes |
| Cattle (dairy only) | 0.381 | 0.571 | 9.90 | 14.85 | Cattle (dairy) | Rye, straw | Yes |
| Sheep (all diets) | 0.780 | 1.201 | 18.36 | 28.27 | Sheep (lamb) | Rye, straw | Yes |
| Sheep (ewe only) | 0.612 | 0.942 | 18.36 | 28.27 | Sheep (ram/ewe) | Rye, straw | Yes |
| Swine (all diets) | 0.145 | 0.145 | 4.85 | 4.85 | Swine (finishing) | Flaxseed/linseed, meal | Yes |
| Poultry (all diets) | 0.442 | 0.612 | 6.46 | 8.94 | Poultry (layer) | Wheat, straw | Yes |
| Poultry (layer only) | 0.442 | 0.612 | 6.46 | 8.94 | Poultry (layer) | Wheat, straw | Yes |

bw: body weight; DM: dry matter.

<sup>(a)</sup>: When one group of livestock includes several subgroups (e.g., poultry ‘all’ including broiler, layer and turkey), the result of the most critical subgroup is identified from the maximum dietary burdens expressed as ‘mg/kg bw per day’.

<sup>(b)</sup>: The most critical commodity is the major contributor identified from the maximum dietary burden expressed as ‘mg/kg bw per day’.
B.2.1. Nature of residues and methods of analysis in livestock

B.2.1.1. Metabolism studies, methods of analysis and residue definitions in livestock

| Livestock (available studies) | Animal | Dose (mg/kg bw/d) | Duration (days) | Comment/source |
|-------------------------------|--------|-------------------|-----------------|----------------|
| Laying hen (available studies)| Laying hen | 18 | 6 | EFSA (2018a,b) |
| Lactating goat (available studies)| Lactating goat | 19 | 5 | EFSA (2018a,b) |

Time needed to reach a plateau concentration in milk and eggs (days)

- Milk: after 3 days
- Eggs: no plateau was reached during the study (6 days), but feeding study indicated that a plateau was reached after 10 days.

Metabolism in rat and ruminant similar

- Yes

Can a general residue definition be proposed for animals?

- Yes

Animal residue definition for monitoring (RD-Mo)

- Sum of mepiquat and its salts, expressed as mepiquat chloride

Animal residue definition for risk assessment (RD-RA)

- Sum of mepiquat, 4-hydroxy-mepiquat and their salts, expressed as mepiquat chloride

Fat soluble residues

- No

Methods of analysis for monitoring of residues (analytical technique, matrix, LOQs)

- HPLC–MS/MS, LOQ: 0.05 mg/kg (as mepiquat chloride), validated in kidney and liver (EFSA, 2008) and in milk, eggs and meat (EFSA, 2013)
- HPLC–MS/MS, LOQ 0.01 mg/kg (expressed as mepiquat chloride), validated in milk, meat, liver, egg and fat (EFSA, 2018b)
- Confirmatory methods available.
- ILVs available

HPLC–MS/MS: high-performance liquid chromatography with tandem mass spectrometry; LOQ: limit of quantification; ILV: independent laboratory validation.
B.2.1.2. Stability of residues in livestock

| Animal products (available studies) | Animal | Commodity                          | T (°C) | Stability period | Compounds covered | Comment/source |
|-------------------------------------|--------|------------------------------------|--------|-----------------|-------------------|---------------|
|                                     | Cow    | Tissues (muscle, fat, liver, kidney)| –18°C  | 26 Months       | Mepiquat chloride | EFSA (2018a,b) |
|                                     | Cow    | Milk                               | –18°C  | 26 Months       | Mepiquat chloride |               |
|                                     | Hen    | Muscle                             | –18°C  | 26 Months       | Mepiquat chloride |               |
|                                     | Hen    | Egg                                | –18°C  | 26 Months       | Mepiquat chloride |               |
|                                     | Cow    | Liver                              | –18°C  | 26 Months       | 4-hydroxy-mepiquat|               |
|                                     | Cow    | Milk                               | –18°C  | 26 Months       | 4-hydroxy-mepiquat|               |

Storage stability of the metabolite 4-hydroxy-mepiquat is only demonstrated in liver and milk. However, as this metabolite is not of concern in the other animal matrices as shown in the metabolism studies, no additional storage stability data are required (EFSA, 2018a,b).

B.2.2. Magnitude of residues in livestock

B.2.2.1. Summary of the residue data from livestock feeding studies

| Animal commodity | Residues at the closest feeding level (mg/kg) | Estimated value at 1N | MRL proposal (mg/kg) | CF |
|------------------|-----------------------------------------------|-----------------------|----------------------|----|
|                  | Mean | Highest | STMR (mg/kg) | HR (mg/kg) |                |
| Cattle (all)     |      |         |              |           |                |
| Closest feeding level: 0.42 mg/kg bw; 0.7 N rate dairy cattle (highest diet)(a) |
| Muscle           | 0.05 | 0.05    | 0.05         | 0.06       | 0.06            | 1.0 |
| Fat              | 0.05 | 0.05    | 0.05         | 0.05       | 0.05            | 1.0 |
| Liver            | 0.14 | 0.19    | 0.20         | 0.29       | 0.3             | 1.7 |
| Kidney           | 0.15 | 0.20    | 0.22         | 0.40       | 0.4             | 1.0 |
| Cattle (dairy only) |     |         |              |           |                |
| Closest feeding level: 0.42 mg/kg bw; 0.7 N rate dairy cattle(a) |
| Milk(b)          | 0.05 | 0.05    | 0.05         | 0.07       | 0.07            | 1.0 |
| Sheep (all)(c)   |      |         |              |           |                |
| Closest feeding level: 0.42 mg/kg bw; 0.3 N rate lamb (highest diet) |
| Muscle           | 0.05 | 0.05    | 0.06         | 0.08       | 0.09            | 1.0 |
| Fat              | 0.05 | 0.05    | 0.05         | 0.06       | 0.06            | 1.0 |
| Liver            | 0.14 | 0.19    | 0.28         | 0.55       | 0.6             | 1.7 |
| Kidney           | 0.15 | 0.20    | 0.36         | 0.65       | 0.7             | 1.0 |
| Sheep (dairy only)(c) |    |         |              |           |                |
| Closest feeding level: 0.42 mg/kg bw; 0.4 N rate ewe(a) |
| Milk(b)          | 0.05 | 0.05    | 0.07         | 0.11       | 0.15            | 1.0 |
| Swine (all)(c)   |      |         |              |           |                |
| Closest feeding level: 0.42 mg/kg bw; 2.9 N rate finishing (highest diet)(a) |
| Muscle           | 0.05 | 0.05    | 0.05         | 0.05       | 0.05            | 1.0 |
| Fat              | 0.05 | 0.05    | 0.05         | 0.05       | 0.05            | 1.0 |
| Liver            | 0.14 | 0.19    | 0.05         | 0.07       | 0.07            | 1.7 |
| Kidney           | 0.15 | 0.20    | 0.05         | 0.07       | 0.07            | 1.0 |
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| Animal commodity          | Residues at the closest feeding level (mg/kg) | Estimated value at 1N | MRL proposal (mg/kg) | CF |
|---------------------------|-----------------------------------------------|-----------------------|----------------------|----|
|                           | Mean | Highest | STMR (mg/kg) | HR (mg/kg) |               |
| **Poultry (all)**         |      |         |             |            |               |
| Closest feeding level: 0.44 mg/kg bw; 0.7 N rate layer<sup>(a)</sup> |      |         |             |            |               |
| Muscle                    | 0.05 | 0.05    | 0.05        | 0.05       | **0.05**     | 1.0 |
| Fat                       | 0.05 | 0.05    | 0.05        | 0.05       | **0.05**     | 1.0 |
| Liver                     | 0.05 | 0.05    | 0.05        | 0.05       | **0.05**     | 1.0 |
| **Poultry (layer only)**  |      |         |             |            |               |
| Closest feeding level: 0.44 mg/kg bw; 0.7 N rate layer<sup>(a)</sup> |      |         |             |            |               |
| Eggs                      | 0.05 | 0.05    | 0.05        | 0.06       | **0.07**     | 1.0 |

MRL: maximum residue level; STMR: supervised trials median residue; HR: highest residue; CF: conversion factor for enforcement to risk assessment residue definition; bw: body weight.

<sup>(a)</sup>: Closest feeding level and N dose rate related to the maximum dietary burden.

B.3. Consumer risk assessment

**ARfD**

0.3 mg/kg bw (EFSA, 2008)

**Highest IESTI, according to EFSA PRIMo**

Milk and milk products, cattle: 2.1% of ARfD
Bovine liver: 1.3% of ARfD
Other commodities: < 1% of ARfD
Cotton seeds: < 0.01% of ARfD

**Assumptions made for the calculations**

Cotton seeds are expected to be bulked; therefore the calculation is based on the supervised trial median residues (STMR). For the animal commodities the highest residues (HR) values multiplied by the relevant conversion factor were used.

**ADI**

0.2 mg/kg bw per day (EFSA, 2008)

**Highest IEDI, according to EFSA PRIMo**

7.6% ADI (WHO Cluster diet B)
Contribution of crops assessed:
Cotton seeds: < 1% of ADI
Animal commodities: < 1% of ADI

**Assumptions made for the calculations**

The calculation is based on the median residue levels in the raw agricultural commodities. The contribution of commodities where no GAP was reported in the framework of the MRL review and subsequent Art 10 MRL assessments were not included in the calculation.

ARfD: acute reference dose; bw: body weight; IESTI: international estimated short-term intake; PRIMo: (EFSA) Pesticide Residues Intake Model; ADI: acceptable daily intake; IEDI: international estimated daily intake; WHO: World Health Organization; MRL: maximum residue level; GAP: Good Agricultural Practice
B.4. Recommended MRLs

| Code(a) | Commodity          | Existing EU MRL(b) / recently proposed amendment(c) (mg/kg) | Proposed EU MRL (mg/kg) | Comment/justification |
|---------|--------------------|---------------------------------------------------------------|--------------------------|----------------------|
| 0401090 | Cotton seeds       | 5 (ft) / not relevant                                         | 6                        | The submitted data are sufficient to derive an MRL proposal. Risk for consumers unlikely |
| 1011010 | Swine muscle       | 0.05*/0.05*                                                   | 0.05                     | MRL proposals based on livestock dietary intake calculation and available feeding studies when considering the contribution of the new intended uses in cotton and the contribution from the feed items assessed in previous EFSA reasoned opinions. Analytical methods for enforcement are available to control the residues of mepiquat chloride in animal commodities at the validated LOQ of 0.01 mg/kg. Risk for consumers unlikely |
| 1011020 | Swine fat tissue   | 0.05*/0.05*                                                   | 0.05                     |
| 1011030 | Swine liver        | 0.05*/0.07                                                    | 0.07                     |
| 1011040 | Swine kidney       | 0.05*/0.07                                                    | 0.07                     |
| 1012010 | Bovine muscle      | 0.09*/0.06                                                   | 0.06                     |
| 1012020 | Bovine fat tissue  | 0.06/0.05                                                   | 0.05                     |
| 1012030 | Bovine liver       | 0.5/0.3                                                      | 0.3                      |
| 1012040 | Bovine kidney      | 0.8/0.4                                                      | 0.4                      |
| 1013010 | Sheep muscle       | 0.09/0.09                                                    | 0.09                     |
| 1013020 | Sheep fat tissue   | 0.06/0.06                                                   | 0.06                     |
| 1013030 | Sheep liver        | 0.5/0.6                                                      | 0.6                      |
| 1013040 | Sheep kidney       | 0.8/0.7                                                      | 0.7                      |
| 1014010 | Goat muscle        | 0.09/0.09                                                    | 0.09                     |
| 1014020 | Goat fat tissue    | 0.06/0.06                                                    | 0.06                     |
| 1014030 | Goat liver         | 0.5/0.6                                                      | 0.6                      |
| 1014040 | Goat kidney        | 0.8/0.7                                                      | 0.7                      |
| 1015010 | Equine muscle      | 0.09/0.06                                                    | 0.06                     |
| 1015020 | Equine fat tissue  | 0.06/0.05                                                    | 0.05                     |
| 1015030 | Equine liver       | 0.5/0.3                                                      | 0.3                      |
| 1015040 | Equine kidney      | 0.8/0.4                                                      | 0.4                      |
| 1016010 | Poultry muscle     | 0.05*/0.05*                                                   | 0.05                     |
| 1016020 | Poultry fat tissue | 0.05*/0.05*                                                   | 0.05                     |
| 1016030 | Poultry liver      | 0.05*/0.05*                                                   | 0.05                     |
| 1020010 | Cattle milk        | 0.06/0.07                                                    | 0.07                     |
| 1020020 | Sheep milk         | 0.06/0.15                                                    | 0.15                     |
| 1020030 | Goat milk          | 0.06/0.15                                                    | 0.15                     |
| 1020040 | Horse milk         | 0.06/0.07                                                    | 0.07                     |
| 1030000 | Birds eggs         | 0.05*/0.07                                                    | 0.07                     |

**Enforcement residue definition:** sum of mepiquat and its salts, expressed as mepiquat chloride

**MRL:** maximum residue level; **LOQ:** limit of quantification.

*: Indicates that the MRL is proposed at the limit of quantification.
## Appendix C – Pesticide Residue Intake Model (PRIMO)

### Mepiquat

| Code no. | LOQ (mg/kg bw): | ADI (mg/kg bw/day): | ARfD (mg/kg bw): |
|----------|-----------------|---------------------|-----------------|
|          | 0.01 proposed LOQ | 0.2                | 0.3             |

**Code no.**

- ADI (mg/kg bw/day): 0.2
- ARfD (mg/kg bw): 0.3
- Source of ADI: EFSA
- Source of ARfD: EFSA
- Year of evaluation: 2008

### Chronic risk assessment - refined calculations

| Commodity / group of commodities | TMDI (mg/kg bw/day) in % of ADI | No of diets exceeding ADI: |
|----------------------------------|----------------------------------|---------------------------|
| Sunflower seed                   | 4.6                              | 0                         |
| Wheat                            | 2.6                              | 0                         |
| Rye                              | 0.9                              | 0                         |
| Sunflower seed                   | 1.0                              | 0                         |
| Wheat                            | 0.8                              | 0                         |
| Linseed                          | 0.7                              | 0                         |
| Sunflower seed                   | 0.6                              | 0                         |
| Wheat                            | 0.6                              | 0                         |
| Rye                              | 0.6                              | 0                         |
| Milk and milk products: Cattle   | 0.6                              | 0                         |
| Wheat                            | 0.6                              | 0                         |
| Rye                              | 0.6                              | 0                         |
| Milk and milk products: Cattle   | 0.6                              | 0                         |
| Wheat                            | 0.6                              | 0                         |
| Rye                              | 0.6                              | 0                         |
| Milk and milk products: Cattle   | 0.6                              | 0                         |
| Wheat                            | 0.6                              | 0                         |
| Rye                              | 0.6                              | 0                         |
| Milk and milk products: Cattle   | 0.6                              | 0                         |
| Wheat                            | 0.6                              | 0                         |
| Rye                              | 0.6                              | 0                         |
| Milk and milk products: Cattle   | 0.6                              | 0                         |
| Wheat                            | 0.6                              | 0                         |
| Rye                              | 0.6                              | 0                         |

**Conclusion:**

The estimated Theoretical Maximum Daily Intakes (TMDI), based on pTMRLs were below the ADI. A long-term intake of residues of Mepiquat is unlikely to present a public health concern.
The acute risk assessment is based on the ADI.

For each commodity the calculation is based on the highest reported MS consumption per kg bw and the corresponding unit weight from the MS with the critical consumption. If no data on the unit weight was available from that MS an average European unit weight was used for the IESTI calculation.

In the IESTI 1 calculation, the variability factors were 10, 7 or 5 (according to JMPR manual 2002), for lettuce a variability factor of 5 was used.

In the IESTI 2 calculations, the variability factors of 10 and 7 were replaced by 5. For lettuce the calculation was performed with a variability factor of 3.

Threshold MRL is the calculated residue level which would lead to an exposure equivalent to 100 % of the ARfD.

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Acute risk assessment / adults / general population - refined calculations

The acute risk assessment is based on the ARfD.

For each commodity the calculation is based on the highest reported MS consumption per kg bw and the corresponding unit weight from the MS with the critical consumption. If no data on the unit weight was available from that MS an average European unit weight was used for the IESTI calculation.

In the IESTI 1 calculation, the variability factors were 10, 7 or 5 (according to JMPR manual 2002), for lettuce a variability factor of 5 was used.

In the IESTI 2 calculations, the variability factors of 10 and 7 were replaced by 5. For lettuce the calculation was performed with a variability factor of 3.

Threshold MRL is the calculated residue level which would lead to an exposure equivalent to 100 % of the ARfD.

Acute risk assessment / children - refined calculations

The acute risk assessment is based on the ARfD.

For each commodity the calculation is based on the highest reported MS consumption per kg bw and the corresponding unit weight from the MS with the critical consumption. If no data on the unit weight was available from that MS an average European unit weight was used for the IESTI calculation.

In the IESTI 1 calculation, the variability factors were 10, 7 or 5 (according to JMPR manual 2002), for lettuce a variability factor of 5 was used.

In the IESTI 2 calculations, the variability factors of 10 and 7 were replaced by 5. For lettuce the calculation was performed with a variability factor of 3.

Threshold MRL is the calculated residue level which would lead to an exposure equivalent to 100 % of the ARfD.

The results of the IESTI calculations are reported for at least 5 commodities. If the ARfD is exceeded for more than 5 commodities, all IESTI values > 90% of ARfD are reported.

For Mepiquat IESTI 1 and IESTI 2 were calculated for food commodities for which pTMRLs were submitted and for which consumption data are available.

No exceedance of the ARfD/ADI was identified for any unprocessed commodity.

For processed commodities, no exceedance of the ARfD/ADI was identified.

Precise results of the calculation are given in Table 1.

Conclusion:

For Mepiquat IESTI 1 and IESTI 2 were calculated for food commodities for which pTMRLs were submitted and for which consumption data are available. No exceedance of the ARfD/ADI was identified for any unprocessed commodity.

No exceedance of the ARfD/ADI was identified for any processed commodity.
Appendix D – Input values for the exposure calculations

D.1. Livestock dietary burden calculations

| Feed commodity                          | Median dietary burden | Maximum dietary burden |
|-----------------------------------------|-----------------------|------------------------|
|                                         | Input value (mg/kg)   | Comment                | Input value (mg/kg) | Comment |
| Risk assessment definition: sum of mepiquat and its salts, expressed as mepiquat chloride |
| Cotton, undelinted seeds                | 1.76                  | STMR                   | 1.76               | STMR    |
| Cotton, meal                            | 3.34                  | STMR × PF (1.9)        | 3.34               | STMR × PF (1.9) |
| Flaxseed/Linseed, meal                  | 18.40                 | STMR × PF (1.6) (EFSA, 2018b) | 18.40 | STMR × PF (1.6) (EFSA, 2018b) |
| Sunflower, meal                         | 23.75                 | STMR × PF (1.9) (EFSA, 2018b) | 23.75 | STMR × PF (1.9) (EFSA, 2018b) |
| Canola (Rape seed), meal                | 5.84                  | STMR × PF (1.6) (EFSA, 2018b) | 5.84 | STMR × PF (1.6) (EFSA, 2018b) |
| Barley, grain                           | 0.73                  | STMR (EFSA, 2015)      | 0.73               | STMR (EFSA, 2015) |
| Brewer’s grain, dried                   | 0.78                  | STMR × PF (1.1) (EFSA, 2015) | 0.78 | STMR × PF (1.1) (EFSA, 2015) |
| Oat, grain                              | 0.73                  | STMR (EFSA, 2015)      | 0.73               | STMR (EFSA, 2015) |
| Rye, grain                              | 0.60                  | STMR (EFSA, 2015)      | 0.60               | STMR (EFSA, 2015) |
| Wheat, grain                            | 0.60                  | STMR (EFSA, 2015)      | 0.60               | STMR (EFSA, 2015) |
| Wheat, distiller’s grain (dry)          | 1.98                  | STMR (EFSA, 2015) × default PF (3.3) | 1.98 | STMR (EFSA, 2015) × default PF (3.3) |
| Wheat, milled by-products               | 1.08                  | STMR (EFSA, 2015) × default PF (1.8) | 1.08 | STMR (EFSA, 2015) × default PF (1.8) |
| Barley, straw                           | 2.34                  | STMR (EFSA, 2015)      | 5.90               | HR (EFSA, 2015) |
| Oat, straw                              | 2.34                  | STMR (EFSA, 2015)      | 5.90               | HR (EFSA, 2015) |
| Wheat, straw                            | 28.30                 | STMR (EFSA, 2015)      | 50.10              | HR (EFSA, 2015) |

STMR: supervised trials median residue; HR: highest residue; PF: processing factor.

D.2. Consumer risk assessment

| Commodity                              | Chronic risk assessment | Acute risk assessment |
|----------------------------------------|-------------------------|-----------------------|
|                                        | Input value (mg/kg)     | Comment               | Input value (mg/kg)     | Comment |
| Risk assessment residue definition for commodities of plant origin: sum of mepiquat and its salts, expressed as mepiquat chloride |
| Cotton seeds                           | 1.76                    | STMR                  | 1.76                    | STMR |
| Cultivated fungi                       | 0.013                   | STMR (EFSA, 2016)     |                        |       |
| Linseed                                | 11.5                    | STMR (EFSA, 2018b)    |                        |       |
| Poppy seed                             | 11.5                    | STMR (EFSA, 2018b)    |                        |       |
| Sunflower seed                         | 12.5                    | STMR (EFSA, 2018b)    |                        |       |
| Rapseed                                | 3.65                    | STMR (EFSA, 2018b)    |                        |       |
| Mustard seed                           | 11.5                    | STMR (EFSA, 2018b)    |                        |       |
| Gold of pleasure                       | 11.5                    | STMR (EFSA, 2018b)    |                        |       |
| Barley and oat grain                   | 0.73                    | STMR (EFSA, 2015)     |                        |       |
| Rye and wheat grain                    | 0.6                     | STMR (EFSA, 2015)     |                        |       |
### Commodity

| Commodity                      | Chronic risk assessment | Acute risk assessment |
|-------------------------------|-------------------------|-----------------------|
|                               | Input value (mg/kg)     | Comment               | Input value (mg/kg) | Comment               |
| Swine muscle                  | 0.05 STMR               |                       | 0.05 HR             |                       |
| Swine fat                     | 0.05 STMR               |                       | 0.05 HR             |                       |
| Swine liver                   | 0.08 STMR × CF (1.7)    | 0.11 HR × CF (1.7)    |                       |                       |
| Swine kidney                  | 0.05 STMR               | 0.07 HR               |                       |                       |
| Bovine and equine muscle      | 0.05 STMR               |                       | 0.06 HR             |                       |
| Bovine and equine fat         | 0.05 STMR               |                       | 0.05 HR             |                       |
| Bovine and equine liver       | 0.35 STMR × CF (1.7)    | 0.5 HR × CF (1.7)     |                       |                       |
| Bovine and equine kidney      | 0.22 STMR               | 0.4 HR                |                       |                       |
| Sheep and goat muscle         | 0.06 STMR               |                       | 0.08 HR             |                       |
| Sheep and goat fat            | 0.05 STMR               |                       | 0.06 HR             |                       |
| Sheep and goat liver          | 0.48 STMR × CF (1.7)    | 0.94 HR × CF (1.7)    |                       |                       |
| Sheep and goat kidney         | 0.36 STMR               | 0.65 HR               |                       |                       |
| Poultry muscle                | 0.05 STMR               | 0.05 HR               |                       |                       |
| Poultry fat                   | 0.05 STMR               |                       | 0.05 HR             |                       |
| Poultry liver                 | 0.05 STMR               |                       | 0.05 HR             |                       |
| Cattle and equine milk        | 0.05 STMR               |                       | 0.05 STMR           |                       |
| Sheep and goat milk           | 0.07 STMR               |                       | 0.07 STMR           |                       |
| Birds’ eggs                   | 0.05 STMR               |                       | 0.06 HR             |                       |

**Risk assessment residue definition for commodities of animal origin:** sum of mepiquat, 4-hydroxy-mepiquat and their salts, expressed as mepiquat chloride.

STMR: supervised trials median residue; HR: highest residue; CF: conversion factor.
### Appendix E – Used compound codes

| Code/trivial name | IUPAC name/SMILES notation/InChiKey\(^{(a)}\) | Structural formula\(^{(b)}\) |
|-------------------|----------------------------------------------|-----------------------------|
| mepiquat          | 1,1-dimethylpiperidinium                    | ![Structural formula](image) |
|                   | C[N-]1(C)CCCCC1                              |                             |
|                   | NNCAWEWCFVZOGF-UHFFFAOYNA-N                 |                             |
| mepiquat chloride | 1,1-dimethylpiperidinium chloride           | ![Structural formula](image) |
|                   | [Cl-].C[N-]1(C)CCCCC1                        |                             |
|                   | VHOVSQVSAQAQANU-UHFFFAOYNA-M                |                             |
| 4-hydroxy-mepiquat chloride | 4-hydroxy-1,1-dimethylpiperidinium chloride | ![Structural formula](image) |
|                   | [Cl-].C[N-]1(C)CCC(O)CC1                    |                             |
|                   | GDFMSGICPAHHIB-UHFFFAOYNA-M                 |                             |

IUPAC: International Union of Pure and Applied Chemistry; SMILES: simplified molecular-input line-entry system; InChiKey: International Chemical Identifier Key.

\(^{(a)}\): ACD/Name 2017.2.1 ACD/Labs 2017 Release (File version N40E41, Build 96719, 6 September 2017).

\(^{(b)}\): ACD/ChemSketch 2017.2.1 ACD/Labs 2017 Release (File version C40H41, Build 99535, 14 February 2018).

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