

APPROVED: 17 August 2015

PUBLISHED: 24 August 2015

doi:10.2903/j.efsa.2015.4214

Review of the existing maximum residue levels (MRLs) for mepiquat according to Article 12 of Regulation (EC) No 396/2005

European Food Safety Authority (EFSA)

Abstract

According to Article 12 of Regulation (EC) No 396/2005, the European Food Safety Authority (EFSA) has reviewed the maximum residue levels (MRLs) currently established at European level for the pesticide active substance mepiquat. In order to assess the occurrence of mepiquat residues in plants, processed commodities, rotational crops and livestock, EFSA considered the conclusions derived in the framework of Directive 91/414/EEC as well as the European authorisations reported by Member States (incl. the supporting residues data). Based on the assessment of the available data, MRL proposals were derived and a consumer risk assessment was carried out. Although no apparent risk to consumers was identified, some information required by the regulatory framework was found to be missing. Hence, the consumer risk assessment is considered indicative only and some MRL proposals derived by EFSA still require further consideration by risk managers.

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Keywords: mepiquat, MRL review, Regulation (EC) No 396/2005, consumer risk assessment, quaternary ammonium compound, plant growth regulator, mepiquat chloride

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Question number: EFSA-Q-2009-00119

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Acknowledgement: EFSA wishes to thank the rapporteur Member State United Kingdom for the preparatory work on this scientific output.

Suggested citation: EFSA (European Food Safety Authority), 2015. Reasoned opinion on the review of the existing maximum residue levels (MRLs) for mepiquat according to Article 12 of Regulation (EC) No 396/2005. EFSA Journal 2015;13(8):4214, 35 pp. doi:10.2903/j.efsa.2015.4214

ISSN: 1831-4732

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Summary

Mepiquat was included in Annex I to Directive 91/414/EEC on 1 March 2009 by Commission Directive 2008/108/EC, and has been deemed to be approved under Regulation (EC) No 1107/2009, in accordance with Commission Implementing Regulation (EU) No 540/2011, as amended by Commission Implementing Regulation (EU) No 541/2011. As the active substance was approved after the entry into force of Regulation (EC) No 396/2005 on 2 September 2008, EFSA is required to provide a reasoned opinion on the review of the existing MRLs for that active substance in compliance with Article 12(1) of the aforementioned regulation. In order to collect the relevant pesticide residues data, EFSA asked United Kingdom, as the designated rapporteur Member State (RMS), to complete the Pesticide Residues Overview File (PROFile) and to prepare a supporting evaluation report. The PROFile and evaluation report provided by the RMS were made available to the Member States. A request for additional information was addressed to the Member States in the framework of a completeness check period which was initiated by EFSA on 21 January 2015 and finalised on 17 March 2015. After having considered all the information provided, EFSA prepared a completeness check report which was made available to Member States on 20 April 2015.

Based on the conclusions derived by EFSA in the framework of Directive 91/414/EEC and the additional information provided by the RMS and Member States, EFSA prepared in June 2015 a draft reasoned opinion, which was circulated to Member States for consultation via a written procedure. Comments received by 9 July 2015 were considered during the finalisation of this reasoned opinion. The following conclusions are derived.

The metabolism of mepiquat has been investigated in three different crop groups as well as in rotational crops. The only relevant compound found in these studies was mepiquat. The metabolic pattern depicted in rotational crops was found to be more extensive than in primary crops but, as no relevant residues were found in the succeeding crops, a specific residue definition was not deemed necessary. Hydrolysis studies demonstrated that mepiquat is stable under processing by pasteurisation, baking/brewing/boiling and sterilisation. Therefore, a general residue definition for both monitoring and risk assessment in all plant commodities was proposed as the sum of mepiquat and its salts, expressed as mepiquat chloride. A validated analytical method for this residue definition in all commodities of plant origin is available.

The available residue trials allowed EFSA assessing the magnitude of residues resulting from the authorised GAPS reported in this review. MRL proposals as well as risk assessment values were derived for all commodities under evaluation, except for linseed and sunflower seed. For rape seed, where additional trials are still required for the most critical GAPS, only a tentative MRL is derived. In addition, studies investigating the magnitude of residues in processed commodities of rapeseed and cereals allowed EFSA to derive robust processing factors for enforcement and risk assessment in crude oil, refined oil, meal/press cake, brewing malt, beer, pot/pearl, bran, whole-meal flour, whole-meal bread and white flour.

Mepiquat is authorised for use in oilseeds and cereals which might be fed to livestock. The metabolism of mepiquat was investigated in lactating goats and laying hens. As metabolic pathways are expected to be similar in ruminants and pigs, the results of the goat metabolism study could be extrapolated to swine. From these studies, EFSA proposed a general residue definition for monitoring of livestock commodities as the sum of mepiquat and its salts, expressed as mepiquat chloride. A validated analytical method for enforcement of the proposed residue definition in commodities of animal origin is available. For risk assessment, the residue definition was set as the sum of mepiquat, 4-hydroxy-mepiquat and their salts, expressed as mepiquat chloride. EFSA was able to derive a conversion factor for monitoring to risk assessment in ruminant liver (1.7) but it was not deemed necessary in all other animal commodities. Based on the ruminant feeding study, MRLs and risk assessment values were derived in ruminants and swine products. For poultry products, the metabolism study was sufficient to conclude that MRLs and risk assessment values could be established at the limit of quantification (LOQ).

Chronic and acute consumer exposure resulting from the authorised uses reported in the framework of this review was calculated using revision 2 of the EFSA Pesticide Residues Intake Model (PRIMo). For those commodities where data were insufficient to derive an MRL, EFSA considered the existing

EU MRL for an indicative calculation. The highest chronic exposure represented 6.6% of the acceptable daily intake (ADI) (WHO Cluster diet B) and the highest acute exposure amounted to 10.3% of the acute reference dose ARfD (sunflower seed).

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Background

Regulation (EC) No 396/2005¹ establishes the rules governing the setting and the review of pesticide maximum residue levels (MRLs) at European level. Article 12(1) of that regulation stipulates that EFSA shall provide within 12 months from the date of the inclusion or non-inclusion of an active substance in Annex I to Directive 91/414/EEC² a reasoned opinion on the review of the existing MRLs for that active substance. As mepiquat was included in Annex I to Council Directive 91/414/EEC on 1 March 2009 by means of Commission Directive 2008/108/EC,³ and has been deemed to be approved under Regulation (EC) No 1107/2009,⁴ in accordance with Commission Implementing Regulation (EU) No 540/2011,⁵ as amended by Commission Implementing Regulation (EU) No 541/2011,⁶ EFSA initiated the review of all existing MRLs for that active substance.

According to the legal provisions, EFSA shall base its reasoned opinion in particular on the relevant assessment report prepared under Directive 91/414/EEC. It should be noted, however, that in the framework of Directive 91/414/EEC only a few representative uses are evaluated, while MRLs set out in Regulation (EC) No 396/2005 should accommodate all uses authorised within the EU, and uses authorised in third countries that have a significant impact on international trade. The information included in the assessment report prepared under Directive 91/414/EEC is therefore insufficient for the assessment of all existing MRLs for a given active substance.

In order to gain an overview of the pesticide residues data that have been considered for the setting of the existing MRLs, EFSA developed the Pesticide Residues Overview File (PROFile). The PROFile is an inventory of all pesticide residues data relevant to the risk assessment and MRL setting for a given active substance. This includes data on:

- the nature and magnitude of residues in primary crops;
- the nature and magnitude of residues in processed commodities;
- the nature and magnitude of residues in rotational crops;
- the nature and magnitude of residues in livestock commodities and;
- the analytical methods for enforcement of the proposed MRLs.

The United Kingdom, the designated rapporteur Member State (RMS) in the framework of Directive 91/414/EEC, was asked to complete the PROFile for mepiquat and to prepare a supporting evaluation report (United Kingdom, 2010). The PROFile and the supporting evaluation report were submitted to EFSA on 25 August 2010 and made available to the Member States. A request for additional information was addressed to the Member States in the framework of a completeness check period which was initiated by EFSA on 21 January 2015 and finalised on 17 March 2015. Additional evaluation reports were submitted by France, the Netherlands, Sweden and the United Kingdom (France, 2015; Netherlands, 2015; Sweden, 2015; United Kingdom, 2015) and after having considered all the information provided by RMS and Member States, EFSA prepared a completeness check report which was made available to all Member States on 20 April 2015. No further clarifications were sought from Member States.

Based on the conclusions derived by EFSA in the framework of Directive 91/414/EEC, and the additional information provided by the Member States, EFSA prepared in June 2015 a draft reasoned

¹ Regulation (EC) No 396/2005 of the European 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.

² 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. Repealed by Regulation (EC) No 1107/2009.

³ Commission Directive 2008/108/EC of 26 November 2008 amending Council Directive 91/414/EEC to include flutolanil, benfluralin, fluaziflam, fuberidazole and mepiquat as active substances. OJ L 317, 27.11.2008, p. 6-13.

⁴ Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC. OJ L 309, 24.11.2009, p. 1-50.

⁵ Commission Implementing Regulation (EU) No 540/2011 of 25 May 2011 implementing Regulation (EC) No 1107/2009 of the European Parliament and of the Council as regards the list of approved active substances. OJ L 153, 11.6.2011, p. 1-186.

⁶ Commission Implementing Regulation (EU) No 541/2011 of 1 June 2011 amending Implementing Regulation (EU) No 540/2011 implementing Regulation (EC) No 1107/2009 of the European Parliament and of the Council as regards the list of approved active substances. OJ L 153, 11.6.2011, p. 187-188.

opinion, which was submitted to Member States for commenting via a written procedure. All comments received by 9 July 2015 were considered by EFSA during the finalisation of the reasoned opinion.

The evaluation report submitted by the RMS (United Kingdom, 2010), and the evaluation reports submitted by Member States France, the Netherlands, Sweden and the United Kingdom (France, 2015; Netherlands, 2015; Sweden, 2015; United Kingdom, 2015) are considered as supporting documents to this reasoned opinion and, thus, are made publicly available.

In addition, key supporting documents to this reasoned opinion are the completeness check report (EFSA, 2015a) and the Member States consultation report (EFSA, 2015b). These reports are developed to address all issues raised in the course of the review, from the initial completeness check to the reasoned opinion.

For the sake of transparency also the chronic and acute exposure calculations for all crops reported in the framework of this review performed using the EFSA Pesticide Residues Intake Model (PRIMO) are made publicly available.

Terms of reference

According to Article 12 of Regulation (EC) No 396/2005, EFSA shall provide a reasoned opinion on:

- the inclusion of the active substance in Annex IV to the Regulation, when appropriate;
- the necessity of setting new MRLs for the active substance or deleting/modifying existing MRLs set out in Annex II or III of the Regulation;
- the inclusion of the recommended MRLs in Annex II or III to the Regulation;
- the setting of specific processing factors as referred to in Article 20(2) of the Regulation.

The active substance and its use pattern

Mepiquat is the ISO common name for 1,1-dimethylpiperidinium (IUPAC). However, this active substance is mainly available on the market as its variant mepiquat chloride which is also covered by the approval of the active substance mepiquat.

Mepiquat is a quaternary ammonium compound which is used as plant growth regulator. Mepiquat acts by inhibiting the biosynthesis of gibberellic acid. It is absorbed and translocated throughout the plant. Mepiquat is used on cereals and certain oilseeds to reduce unwanted longitudinal shoot growth without lowering plant productivity.

The chemical structure of the active substance and its main metabolites are reported in Appendix E.

Mepiquat was evaluated in the framework of Directive 91/414/EEC with the United Kingdom designated as rapporteur Member State (RMS). The representative use supported for the peer review process was as plant growth regulator in cereals for stem stabilisation. Following the peer review, which was carried out by EFSA, a decision on inclusion of the active substance in Annex I to Directive 91/414/EEC was published by means of Commission Directive 2008/108/EC, which entered into force on 1 March 2009. According to Regulation (EU) No 540/2011, mepiquat is deemed to have been approved under Regulation (EC) No 1107/2009. This approval is restricted to uses as plant growth regulator only.

The EU MRLs for mepiquat are established in Annex IIIA of Regulation (EC) No 396/2005 and codex maximum residue limits (CXLs) for this active substance are not available. An overview of the MRL changes that occurred since the entry into force of the abovementioned regulation is provided below.

Table 1: Overview of the MRL changes since the entry into force of Regulation (EC) No 396/2005

Procedure	Legal implementation	Remarks
MRL application (EFSA, 2013)	Commission Regulation (EU) No 36/2014	Oats, wheat and products of animal origin

For the purpose of this MRL review, the critical uses of mepiquat currently authorised within the EU have been collected by the RMS and reported in the PROFile. The additional GAPs reported by Member States during the completeness check were also considered. The details of the authorised GAPs for mepiquat are given in Appendix A. The RMS did not report any use authorised in third countries that might have a significant impact on international trade.

Assessment

EFSA has based its assessment on the evaluation report accompanying the PROFile (United Kingdom, 2010), the Draft Assessment Report (DAR) and its addenda prepared under Council Directive 91/414/EEC (United Kingdom, 2008), the conclusion on the peer review of the pesticide risk assessment of the active substance mepiquat (EFSA, 2008), the previous reasoned opinion on mepiquat (EFSA, 2013) as well as the evaluation reports submitted during the completeness check (France, 2015; Netherlands, 2015; Sweden, 2015; United Kingdom, 2015). The assessment is performed in accordance with the legal provisions of the uniform principles for evaluation and authorisation of plant protection products as set out in Commission Regulation (EU) No 546/2011⁷ and the currently applicable guidance documents relevant for the consumer risk assessment of pesticide residues (European Commission, 1996, 1997a-g, 2000, 2010a, b, 2011 and OECD, 2011).

More detailed information on the available data and on the conclusions derived by EFSA can be retrieved from the list of end points reported in Appendix B. It is highlighted that the variant mepiquat chloride was generally used in the reported studies. Therefore, unless explicitly specified, active substance, application rates and residue levels refer to mepiquat chloride.

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 mepiquat residues in primary crops has been investigated in three different crop groups which are cereals, pulses and oilseeds and fruit crops (EFSA, 2008). In the framework of the present review, an additional study performed on rape seed was also provided by France (France, 2015). In all these studies, the only relevant component of the residues at harvest was the parent compound (72 to 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 ($\leq 6\%$ TRR).

1.1.2. Nature of residues in rotational crops

A confined rotational crop study using wheat, radish and lettuce planted in soil treated with mepiquat was assessed during the peer review (EFSA, 2008). It is noted that the experiments were performed with a slightly lower application rate compared to the most critical good agricultural practices (GAPs) reported for cereals (0.9N) and linseed (0.75N). However, as the treatments were made on bare soil, it is assumed that the dose applied in the study is comparable to the doses received on soil in practice, considering the possible interception by cereal and linseed crops. 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. Mepiquat chloride was found to remain below the limit of quantification (LOQ) of 0.01 mg/kg. The remaining extractable radioactivity was associated to

⁷ Commission Regulation (EU) No 546/2011 of 10 June 2011 implementing Regulation (EC) No 1107/2009 of the European Parliament and of the Council as regards uniform principles for evaluation and authorisation of plant protection products. OJ L 155, 11.06.2011, p. 127-175.

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 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.

1.1.3. Nature of residues in processed commodities

The effect of processing on the nature of mepiquat was also investigated in the framework of the peer review. Studies were conducted simulating representative hydrolytic conditions for pasteurisation (20 minutes at 90°C, pH 4), boiling/brewing/baking (60 minutes at 100°C, pH 5) and sterilisation (20 minutes at 120°C, pH 6). From these studies, it was concluded that processing by pasteurisation, baking/brewing/boiling and sterilisation is not expected to have a significant impact on the composition of residues in matrices of plant origin (EFSA, 2008).

1.1.4. Methods of analysis in plants

During the peer review, an analytical method using HPLC with tandem mass spectrometry detection (HPLC-MS/MS) was validated for the determination of mepiquat in the four main crop groups with an LOQ of 0.05 mg/kg (as mepiquat chloride). Since the method is highly specific for mepiquat and its salts, a separate confirmatory method is not required. An independent laboratory validation ILV is available for three different matrices (EFSA, 2008).

According to the EU Reference Laboratories (EURLs), an LOQ of 0.01 mg/kg (as mepiquat cation) can be achieved in high water and acidic commodities and an LOQ of 0.02 mg/kg (as mepiquat cation) can be achieved in fatty and dry commodities. Nevertheless, the validation data supporting this statement are not available (EFSA, 2015b).

Hence, it is concluded that mepiquat can be enforced in commodities of plant origin with an LOQ of 0.05 mg/kg (as mepiquat chloride).

1.1.5. Stability of residues in plants

During the peer review, storage stability of mepiquat was demonstrated for a period of 24 months at –20°C in commodities with high water content (wheat forage) and dry commodities (wheat grain) (EFSA, 2008). Additional studies covering the stability of mepiquat for a period of 25 months at –5°C (and –15°C) in high oil content commodities (cotton seed) were provided during this review (France, 2015; United Kingdom, 2015).

1.1.6. Proposed residue definitions

Based on all this information, it was already concluded in the framework of the peer review that 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. It is highlighted that the proposed residue definition was not yet legally implemented but it is still considered as the most relevant by EFSA and is therefore confirmed.

1.2. Magnitude of residues in plants

1.2.1. Magnitude of residues in primary crops

To assess the magnitude of mepiquat residues resulting from the reported GAPs, EFSA considered all residue trials reported by the RMS in its evaluation report (United Kingdom, 2010), including residue trials evaluated in the framework of the peer review (EFSA, 2008) or in the framework of a previous MRL application (EFSA, 2013) and additional data submitted during the completeness check (France, 2015; Netherlands, 2015; Sweden, 2015; United Kingdom, 2015). All residue trial samples considered in this framework were stored in compliance with the demonstrated storage conditions. Decline of residues during storage of the trial samples is therefore not expected.

The number of residue trials and extrapolations were evaluated in accordance with the European guidelines on comparability, extrapolation, group tolerances and data requirements for setting MRLs (European Commission, 2011).

For two crops reported during this review (linseed and sunflower seed), residue trials were not available to support the authorisations. Moreover, the GAPs reported for these crops were not adequately reported since several parameters were missing (number of applications and pre-harvest interval (PHI) or growth stage at application). Therefore, MRL or risk assessment values for these crops could not be derived by EFSA and the following data gaps were identified:

- Linseed: a detailed description of the northern GAP (including number of applications and PHI or growth stage at application) and 4 trials compliant with this GAP are required.
- Sunflower seed: a detailed description of the northern and southern GAPs (including number of applications and PHI or growth stage at application) and 8 trials compliant with each of these GAPs are required.

For rape seed, the reported residue trials reported were only sufficient to derive tentative MRL and risk assessment values. The following considerations were made:

- Rape seed (southern European Union (SEU)): the number of residue trials supporting the southern outdoor GAP is not compliant with the data requirements for this crop (4 trials instead of 8). Although tentative MRL and risk assessment values can be derived, 4 additional trials compliant with the southern GAP are still required.
- Rape seed (northern European Union (NEU)): the GAP considered in this review is supported by data but a more critical GAP, reported by Belgium and Germany, is also authorised and not supported by data. Therefore, 8 residue trials compliant with the Belgian and German GAP are also required.

For all other crops under consideration, available residue trials are sufficient to derive MRL and risk assessment values, taking note of the following considerations:

- Wheat (grain and straw): the number of residue trials supporting the southern outdoor GAP is not compliant with the data requirements for this crop (7 trials instead of 8). However, appropriate MRL and risk assessment values can be derived from the northern GAP (which is more critical). Therefore, additional data are not required for the southern GAP authorised on wheat.
- Barley (grain and straw): the number of residue trials supporting the southern outdoor GAP is not compliant with the data requirements for this crop (7 trials instead of 8). However, appropriate MRL and risk assessment values can be derived from the northern GAP (which is more critical). Therefore, additional data are not required for the southern GAP authorised on barley.
- Oats (grain and straw): residue trials compliant with the southern GAP are not available while appropriate MRL and risk assessment values can be derived from the northern GAP. As the application rate authorised in the southern GAP is two times lower than in the northern GAP, EFSA acknowledges that the southern GAP is probably less critical than the northern GAP. However, as mepiquat is a plant growth regulator and is applied early during the growth of the crops (BBCH 39), uncertainty remains on the residue levels arising from the southern GAP. Therefore, 8 residue trials compliant with the southern GAP on oats are still required.

1.2.2. Magnitude of residues in rotational crops

Based on the confined rotational crop study evaluated during the peer review (see also section 1.1.2.), significant residues are not expected in the succeeding crops. Rotational crop field trials are therefore not required.

1.2.3. Magnitude of residues in processed commodities

Studies investigating the magnitude of residues in processed commodities of rapeseed and cereals were reported in the framework of the peer review (EFSA, 2008) and during the present review

(France, 2015). An overview of all available processing studies is available in Appendix B1.2.3. Robust processing factors for enforcement and risk assessment were derived in crude oil, refined oil, meal/press cake, brewing malt, beer, pot/pearl, bran, whole-meal flour, whole-meal bread and white flour.

Further processing studies are not required as they are not expected to affect the outcome of the risk assessment. However, if processing factors were to be required by risk managers, in particular for enforcement purposes, additional processing studies would be needed.

1.2.4. Proposed MRLs

Consequently, the available residues data are considered sufficient to derive MRL proposals as well as risk assessment values for all commodities under evaluation, except for linseed and sunflower seed where the available data were insufficient. For rape seed, where additional trials are still required for the most critical GAPs, only a tentative MRL is derived. Tentative MRLs were also derived for cereal straw in view of the future need to set MRLs in feed items.

2. Residues in livestock

Mepiquat is authorised for use on oilseeds and small grain cereals that might be fed to livestock. Livestock dietary burdens were therefore calculated for different groups of livestock using the agreed European methodology (European Commission, 1996). The input values for all relevant commodities have been selected according to the recommendations of Joint FAO/WHO Meeting on Pesticide Residues (JMPR) (FAO, 2009) and are summarised in Appendix C1. For rape seed meal and for cereal bran, the processing factors derived under section 1.2.3 have been included in the calculation. The calculated dietary burdens for all groups of livestock were found to exceed the trigger value of 0.1 mg/kg dry matter (DM). Behaviour of residues was therefore assessed in all commodities of animal origin.

It is highlighted that for linseed and cotton seed, no residue data were available. The animal intake of mepiquat residues via these commodities has therefore not been assessed and may have been underestimated. However, this is not expected to have a major impact on the outcome of the dietary burden considering the high contribution of rapeseed meal and cereals.

2.1. Nature of residues and methods of analysis in livestock

During the peer review, the metabolism of mepiquat chloride was evaluated in lactating goat and laying hens (EFSA, 2008). Mepiquat chloride was the major component of the residues in all animal tissues (54–99% TRR), milk (44% TRR) and eggs (70% TRR). The only compound identified in significant levels was the metabolite 4-hydroxy mepiquat-chloride (see Appendix E). It accounted for 6.90 mg eq/kg (40% TRR) in ruminant liver, which is in the same range as the parent compound (9.38 mg/kg). During the peer review, this metabolite was considered to have similar mammalian toxicity as mepiquat chloride. Other metabolites, such as methylpiperidine (see Appendix E), were also identified in tissues but they represented less than 10% of the TRR or less 0.1 mg eq/kg. Moreover, considering the overdosing factor of the metabolism study (15N compared to the calculated dietary burden of meat ruminants), these compounds are expected to remain insignificant upon realistic exposure. In ruminant milk, most of the remaining radioactivity was found to be associated with proteins, fats and carbohydrates (53% TRR), indicating the fragmentation of the ring and the natural incorporation of these fragments into proteins, fats and carbohydrates.

Consequently, EFSA proposed a general residue definition for monitoring of livestock commodities as the sum of mepiquat and its salts, expressed as mepiquat chloride. It is highlighted that the proposed residue definition was not yet legally implemented but it is still considered as the most relevant by EFSA and is therefore confirmed. The metabolism studies provide also evidence that the residues are not accumulating in fat and therefore mepiquat is not classified as fat-soluble.

For risk assessment, the residue definition should also include the metabolite 4-hydroxy mepiquat-chloride and is therefore proposed as the sum of mepiquat, 4-hydroxy mepiquat and their salts, expressed as mepiquat chloride (EFSA, 2008). The available metabolism study allowed EFSA to derive conversion factor of 1.7 for monitoring to risk assessment in ruminant liver. In all other animal

commodities, where the parent compound is the sole significant component of the TRR, a conversion factor of 1 is deemed sufficient.

During the peer review under Directive 91/414/EEC, an analytical method using HPLC-MS/MS for the determination of mepiquat residues was validated with an LOQ of 0.05 mg/kg in liver and kidney; validation data were missing for milk, egg, fat and muscle (EFSA, 2008). These data were presented and evaluated in the framework of an MRL application (EFSA, 2013) and the analytical procedure was successfully validated by an independent laboratory. During the completeness check of mepiquat, it was confirmed that the LOQ refers to mepiquat chloride (EFSA, 2015a). Hence, a validated analytical method for enforcement of the proposed residue definition in commodities of animal origin is available, with an LOQ of 0.05 mg/kg in all matrices. According to the EURLs, LOQs of 0.01 and 0.02 mg/kg (as mepiquat cation) can be achieved in commodities of animal origin but the validation data supporting this statement are not available (EFSA, 2015b).

Storage stability of mepiquat was demonstrated for a period of 26 months at -18°C in all commodities of animal origin.

2.2. Magnitude of residues in livestock

During the peer review, a validated feeding study investigating the magnitude of mepiquat residues in lactating cows was reported (EFSA, 2013). Three dose levels were tested (0.42, 2.09 and 6.26 mg mepiquat chloride/kg body weight (bw) per day). All samples were stored in compliance with the demonstrated storage conditions and a decline of residues during storage of the samples is therefore not expected. Results of this study allowed EFSA to derive MRLs and risk assessment values for ruminants and swine products, in compliance with the latest recommendations on this matter (FAO, 2009). The overview of the study results used to derive the risk assessment values and the MRL proposals are summarised in Appendix B2.2.

In the metabolism study performed in laying hens, highest residue levels were found in kidney (2.8 mg eq./kg), liver (1.4 mg eq./kg) and eggs (1.3 mg eq./kg); levels in fat and muscle were lower (0.28 and 0.31 mg eq./kg, respectively). Therefore, after exposure to the maximum dietary burden (about 360 times lower than the dose level of the metabolism study), residue levels in poultry commodities are expected to remain below the enforcement LOQ of 0.05 mg/kg in eggs and all tissues. Furthermore, a feeding study performed on laying hens (dose levels of 0.06, 0.32 and 0.95 mg mepiquat/kg) also confirmed this finding. Consequently, MRLs and risk assessment values for the relevant commodities in poultry can be established at the LOQ level.

3. Consumer risk assessment

Chronic and acute exposure calculations for all crops reported in the framework of this review were performed using revision 2 of the EFSA PRIMo (EFSA, 2007). Input values for the exposure calculations were derived in compliance with the decision tree reported in Appendix D. Hence, for those commodities where a (tentative) MRL could be derived by EFSA in the framework of this review, input values were median and highest residue values were derived according to the internationally agreed methodologies (FAO, 2009). For those commodities where data were insufficient to derive an MRL in section 3, EFSA considered the existing EU MRL for an indicative calculation. All input values included in the exposure calculations are summarised in Appendix C.

The exposures calculated were compared with the toxicological reference values for mepiquat (chloride), derived by EFSA (2008) under Directive 91/414/EEC. The highest chronic exposure was calculated for World Health Organization (WHO) Cluster diet B, representing 6.6% of the ADI, and the highest acute exposure was calculated for sunflower seed, representing 10.3% of the ARfD. Although uncertainties remain due to the data gaps identified in the previous sections, this indicative exposure calculation did not indicate a risk to consumers.

Conclusions

The metabolism of mepiquat has been investigated in three different crop groups as well as in rotational crops. The only relevant compound found in these studies was mepiquat. The metabolic

pattern depicted in rotational crops was found to be more extensive than in primary crops but, as no relevant residues were found in the succeeding crops, a specific residue definition was not deemed necessary. Hydrolysis studies demonstrated that mepiquat is stable under processing by pasteurisation, baking/brewing/boiling and sterilisation. Therefore, a general residue definition for both monitoring and risk assessment in all plant commodities was proposed as the sum of mepiquat and its salts, expressed as mepiquat chloride. A validated analytical method for this residue definition in all commodities of plant origin is available.

The available residue trials allowed EFSA assessing the magnitude of residues resulting from the authorised GAPs reported in this review. MRL proposals as well as risk assessment values were derived for all commodities under evaluation, except for linseed and sunflower seed. For rape seed, where additional trials are still required for the most critical GAPs, only a tentative MRL is derived. In addition, studies investigating the magnitude of residues in processed commodities of rapeseed and cereals allowed EFSA to derive robust processing factors for enforcement and risk assessment in crude oil, refined oil, meal/press cake, brewing malt, beer, pot/pearl, bran, whole-meal flour, whole-meal bread and white flour.

Mepiquat is authorised for use in oilseeds and cereals which might be fed to livestock. The metabolism of mepiquat was investigated in lactating goats and laying hens. As metabolic pathways are expected to be similar in ruminants and pigs, the results of the goat metabolism study could be extrapolated to swine. From these studies, EFSA proposed a general residue definition for monitoring of livestock commodities as the sum of mepiquat and its salts, expressed as mepiquat chloride. A validated analytical method for enforcement of the proposed residue definition in commodities of animal origin is available. For risk assessment, the residue definition was set as the sum of mepiquat, 4-hydroxy-mepiquat and their salts, expressed as mepiquat chloride. EFSA was able to derive a conversion factor for monitoring to risk assessment in ruminant liver (1.7) but it was not deemed necessary in all other animal commodities. Based on the ruminant feeding study, MRLs and risk assessment values were derived in ruminants and swine products. For poultry products, the metabolism study was sufficient to conclude that MRLs and risk assessment values could be established at the LOQ.

Chronic and acute consumer exposure resulting from the authorised uses reported in the framework of this review was calculated using revision 2 of the EFSA PRIMo. For those commodities where data were insufficient to derive an MRL, EFSA considered the existing EU MRL for an indicative calculation. The highest chronic exposure represented 6.6% of the ADI (WHO Cluster diet B) and the highest acute exposure amounted to 10.3% of the ARfD (sunflower seed).

Recommendations

MRL recommendations were derived in compliance with the decision tree reported in Appendix D of the reasoned opinion (see summary table). All MRL values listed as 'Recommended' in the table are sufficiently supported by data and are therefore proposed for inclusion in Annex II to the Regulation. The remaining MRL values listed in the table are not recommended for inclusion in Annex II because they require further consideration by risk managers (see summary table footnotes for details). In particular, some tentative MRLs and existing EU MRLs need to be confirmed by the following data:

- Further details regarding the authorised GAPs on linseed and sunflower seed;
- Additional trials supporting authorisations on linseed, sunflower seed and rape seed.

It is highlighted that some of the MRLs derived result from a GAP in one climatic zone only, while other GAPs were not fully supported by data. EFSA therefore identified the following data gap which is not expected to impact on the validity of the MRLs derived but which might have an impact on national authorisations:

- 8 residue trials supporting the southern GAP on oats (grain and straw).

If the above reported data gaps are not addressed in the future, Member States are recommended to withdraw or modify the relevant authorisations at national level.

Table 2: Summary table

Code number	Commodity	Existing EU MRL (mg/kg)	Outcome of the review	
			MRL (mg/kg)	Comment
Enforcement residue definition (existing): mepiquat				
Enforcement residue definition (proposed): sum of mepiquat and its salts, expressed as mepiquat chloride				
401010	Linseed	0.05*	0.05*	Further consideration needed ^(a)
401050	Sunflower seed	10	10	Further consideration needed ^(a)
401060	Rape seed	3	4	Further consideration needed ^(b)
500010	Barley grain	3	4	Recommended ^(c)
500050	Oats grain	2	3	Recommended ^(c)
500070	Rye grain	3	3	Recommended ^(c)
500090	Wheat grain	3	3	Recommended ^(c)
1011010	Swine muscle	0.05*	0.05*	Recommended ^(c)
1011020	Swine fat (free of lean meat)	0.05*	0.05*	Recommended ^(c)
1011030	Swine liver	0.05*	0.05*	Recommended ^(c)
1011040	Swine kidney	0.05*	0.05*	Recommended ^(c)
1012010	Bovine muscle	0.08	0.09	Recommended ^(c)
1012020	Bovine fat	0.05*	0.06	Recommended ^(c)
1012030	Bovine liver	0.4	0.5	Recommended ^(c)
1012040	Bovine kidney	0.6	0.8	Recommended ^(c)
1013010	Sheep muscle	0.08	0.09	Recommended ^(c)
1013020	Sheep fat	0.05*	0.06	Recommended ^(c)
1013030	Sheep liver	0.4	0.5	Recommended ^(c)
1013040	Sheep kidney	0.6	0.8	Recommended ^(c)
1014010	Goat muscle	0.08	0.09	Recommended ^(c)
1014020	Goat fat	0.05*	0.06	Recommended ^(c)
1014030	Goat liver	0.4	0.5	Recommended ^(c)
1014040	Goat kidney	0.6	0.8	Recommended ^(c)
1016010	Poultry muscle	0.05*	0.05*	Recommended ^(c)
1016020	Poultry fat	0.05*	0.05*	Recommended ^(c)
1016030	Poultry liver	0.05*	0.05*	Recommended ^(c)
1020010	Cattle milk	0.1	0.06	Recommended ^(c)
1020020	Sheep milk	0.05*	0.06	Recommended ^(c)
1020030	Goat milk	0.05*	0.06	Recommended ^(c)
1030000	Birds' eggs	0.05*	0.05*	Recommended ^(c)
-	Other commodities of plant and animal origin	-	-	Further consideration needed ^(d)

(*): Indicates that the MRL is set at the limit of quantification; (-): Indicates none

(a): GAP evaluated at EU level is not supported by data but no risk to consumers was identified for the existing EU MRL; no CXL is available (combination C-I in Appendix D).

(b): Tentative MRL is derived from a GAP evaluated at EU level, which is not fully supported by data but for which no risk to consumers was identified; no CXL is available (combination E-I in Appendix D).

(c): MRL is derived from a GAP evaluated at EU level, which is fully supported by data and for which no risk to consumers is identified; no CXL is available (combination G-I in Appendix D).

(d): There are no relevant authorisations or import tolerances reported at EU level; no CXL is available. Either a specific LOQ or the default MRL of 0.01 mg/kg may be considered (combination A-I in Appendix D).

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Abbreviations

a.s.	active substance
ADI	acceptable daily intake
ARfD	acute reference dose
BBCH	growth stages of mono- and dicotyledonous plants
bw	body weight
CAS	Chemical Abstract Service
CF	conversion factor for enforcement residue definition to risk assessment residue definition
CXL	codex maximum residue limit
d	day
DAR	Draft Assessment Report (prepared under Council Directive 91/414/EEC)
DAT	days after treatment
DB	dietary burden
DM	dry matter
DT ₉₀	period required for 90 percent dissipation (define method of estimation)
EC	European Commission
eq	residue expressed as a.s. equivalent
EURLs	EU Reference Laboratories (former CRLs)
FAO	Food and Agriculture Organisation of the United Nations
GAP	good agricultural practice
HPLC-MS/MS	high performance liquid chromatography with tandem mass spectrometry
ILV	independent laboratory validation
ISO	International Organisation for Standardization
IUPAC	International Union of Pure and Applied Chemistry
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
LOQ	limit of quantification
MRL	maximum residue level
MS	Member States
NEU	northern European Union
OECD	Organisation for Economic Co-operation and Development
PF	processing factor
PHI	pre-harvest interval
P _{ow}	partition coefficientn-octanol/water
PRIMo	(EFSA) Pesticide Residues Intake Model
PROFile	(EFSA) Pesticide Residues Overview File
R _{ber}	statistical calculation of the MRL by using a non-parametric method

R _{max}	statistical calculation of the MRL by using a parametric method
RA	risk assessment
RAC	raw agricultural commodity
RD	residue definition
RMS	rapporteur Member State
SEU	southern European Union
TRR	total radioactive residue
WHO	World Health Organization

Appendix A – Summary of authorised uses considered for the review of MRLs

Summary of authorised uses to be considered for the review of MRLs

Critical outdoor GAPS for Northern Europe																			
Common name	Crop Scientific name	Region	Outdoor/Indoor	Member state or country	Pest controlled	Formulation			Method	Application						PHI or waiting period (days)	Comments (max. 250 characters)		
						Type	Content			Growth stage	Number		Interval (days)		Rate				
							Conc.	Unit			From BBCH	Until BBCH	Min.	Max.	Min.			Max.	Min.
Linseed	<i>Linum usitatissimum</i>	NEU	Outdoor	FR	Stem stabilisation	SL	305.0	g/L	Foliar treatment - spraying							0.92	kg a.i./ha	GAP not sufficiently detailed by FR.	
Sunflower seed	<i>Helianthus annuus</i>	NEU	Outdoor	FR	Stem stabilisation	SL	305.0	g/L	Foliar treatment - spraying							0.46	kg a.i./ha	GAP not sufficiently detailed by FR.	
Rape seed	<i>Brassica napus</i>	NEU	Outdoor	FR, UK	Stem stabilisation	SL	210.0	g/L	Foliar treatment - spraying	14	59		1			0.29	kg a.i./ha	80	The most critical GAP is authorised in BE and DE (with an application rate of 0.92 kg as/ha) but is not supported by data. In FR, split application is authorised (see Southern FR GAP for details).
Barley	<i>Hordeum spp.</i>	NEU	Outdoor	BE, DE, UK, LU	Stem stabilisation	SL	305.0	g/L	Foliar treatment - spraying	31	49		1			0.76	kg a.i./ha	n.a.	
Oats	<i>Avena fatua</i>	NEU	Outdoor	FI	Stem stabilisation	SL	305.0	g/L	Foliar treatment - spraying	32	39		1			0.61	kg a.i./ha	n.a.	
Rye	<i>Secale cereale</i>	NEU	Outdoor	BE, DE, SE, UK	Stem stabilisation	SL	305.0	g/L	Foliar treatment - spraying	31	49		1			0.76	kg a.i./ha	n.a.	
Wheat	<i>Triticum aestivum</i>	NEU	Outdoor	BE, DE, UK, FR	Stem stabilisation	SL	305.0	g/L	Foliar treatment - spraying	31	49		1			0.76	kg a.i./ha	n.a.	

Critical outdoor GAPs for Southern Europe

Crop		Region	Outdoor/ Indoor	Member state or country	Pest controlled	Formulation			Application							PHI or waiting period (days)	Comments (max. 250 characters)			
Common name	Scientific name					Type	Content		Method	Growth stage		Number		Interval (days)				Rate		
							Conc.	Unit		From BBCH	Until BBCH	Min.	Max.	Min.	Max.			Min.	Max.	Unit
Sunflower seed	<i>Helianthus annuus</i>	SEU	Outdoor	FR	Stem stabilisation	SL	305.0	g/L	Foliar treatment - spraying							0.46	kg a.i./ha		GAP not sufficiently detailed by FR.	
Rape seed	<i>Brassica napus</i>	SEU	Outdoor	FR	Stem stabilisation	SL	210.0	g/L	Foliar treatment - spraying	14	53	1	15			0.29	kg a.i./ha	80	Split application is possible provided that the total app. Rate does not exceed 0.29 kg as/ha.	
Barley	<i>Hordeum spp.</i>	SEU	Outdoor	FR	Stem stabilisation	SL	305.0	g/L	Foliar treatment - spraying	32	39	1				0.76	kg a.i./ha	52	Critical GAP is for winter barley. A less critical GAP is authorised on spring barley (1 x 0.46 kg as/ha).	
Oats	<i>Avena fatua</i>	SEU	Outdoor	FR	Stem stabilisation	SL	300.0	g/L	Foliar treatment - spraying	30	39	1				0.30	kg a.i./ha	n.a.		
Wheat	<i>Triticum aestivum</i>	SEU	Outdoor	FR	Stem stabilisation	SL	305.0	g/L	Foliar treatment - spraying	31	49	1				0.76	kg a.i./ha	56		

a.i.: active ingredient; ha: hectare; NEU: northern European Union; SEU: southern European Union

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

Primary crops (available studies)	Crop groups	Crop(s)	Application(s)	Sampling (DAT)
	Fruit crops	Grapes	Foliar, 2 x 1.1 kg a.s./ha	98
	Cereals/grass crops	Wheat	Foliar, 1 x 0.7 kg a.s./ha	0, 8, 71
		Barley	Foliar, 1 x 0.91 kg a.s./ha	16, 37, 52
	Pulses/Oilseeds	Cotton	Foliar, 1 x 0.16 kg a.s./ha	15, 67
		Rape seed	Foliar, 2 x 0.3 kg a.s./ha	63
For grapes, wheat, barley and cotton, source: United Kingdom, 2005. Study on grapes and cotton were performed in the USA. For rape seed, source: France, 2015.				
Rotational crops (available studies)	Crop groups	Crop(s)	Application(s)	PBI (DAT)
	Root/tuber crops	Radish	Bare soil, 0.7 kg a.s./ha	29, 120, 365
	Leafy crops	Lettuce	Bare soil, 0.7 kg a.s./ha	29, 120, 365
	Cereal	Wheat	Bare soil, 0.7 kg a.s./ha	29, 120, 365
	Source: United Kingdom, 2005			
Processed commodities (hydrolysis study)	Conditions			Investigated?
	Pasteurisation (20 min, 90°C, pH 4)			Yes
	Baking, brewing and boiling (60 min, 100°C, pH 5)			Yes
	Sterilisation (20 min, 120°C, pH 6)			Yes
	Source: EFSA, 2008			

a.s.: active substance; DAT: days after treatment; PBI: plant back interval

Can a general residue definition be proposed for primary crops?
 Rotational crop and primary crop metabolism similar?
 Residue pattern in processed commodities similar to residue pattern in raw commodities?
 Plant residue definition for monitoring (RD-Mo)
 Plant residue definition for risk assessment (RD-RA)
 Conversion factor (monitoring to risk assessment)
 Methods of analysis for monitoring of residues (analytical technique, crop groups, LOQs)

Yes
Yes
Yes
Sum of mepiquat and its salts, expressed as mepiquat chloride
Sum of mepiquat and its salts, expressed as mepiquat chloride
Not relevant
HPLC-MS/MS; LOQ: 0.05 mg/kg (as mepiquat chloride). Validated in high water, high acid, high oil and dry commodities) (EFSA, 2008).

B.1.1.2. Stability of residues in plants

Plant products (available studies)	Category	Commodity	T (°C)	Stability (Months/years)
	High water content	Wheat forage	-20	24 months
	High oil content	Cotton seed	-5	25 months
	Dry/High protein	Wheat grain	-20	24 months
For high water and dry commodities, source: EFSA, 2008.				
For high oil content commodities, source: France, 2015; United Kingdom, 2015.				

B.1.2. Magnitude of residues in plants

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

Crop	Region/ Indoor (a)	Residue levels observed in the supervised residue trials relevant to the supported GAPs (mg/kg)	Recommendations/comments (OECD calculations)	MRL proposals (mg/kg)	HR (mg/kg) (b)	STMR (mg/kg) (c)
Linseed	NEU	-	No data available. Moreover, the authorised GAP is not adequately reported.	-	-	-
Sunflower seed	NEU	-	No data available. Moreover, the authorised GAP is not adequately reported.	-	-	-
	SEU	-		-	-	-
Rape seed	NEU	0.21; 0.47; 0.61; 0.61; 0.76; 0.97; 1.14; 1.38; 1.88	Trials performed with 2 applications instead of 1, all other parameters compliant with GAP (France, 2015; United Kingdom, 2015); the first application is not expected to impact on the final residue. MRL _{OECD} = 2.94 Rber = 2.52 Rmax = 2.45	3	1.88	0.76
	SEU	1.1; 1.2; 1.3; 1.5	Trials performed with 2 applications instead of 1, all other parameters compliant with GAP (France, 2015); the first application is not expected to impact on the final residue. MRL _{OECD} = 3.83 Rber = 2.90 Rmax = 2.15	4 (tentative)	1.50	1.25
Barley grain	NEU	0.09; 0.39; 0.45; 0.53; 0.55; 0.73; 0.75; 0.94; 1.00; 1.16; 1.50	Trials on barley compliant with GAP (EFSA, 2008; France, 2015). MRL _{OECD} = 2.32 Rber = 2.00 Rmax = 1.85	3	1.50	0.73
	SEU	<0.05; <0.05; 0.13; 0.2; 0.76; 1.26; 1.72	Trials on barley compliant with GAP (France, 2015). MRL _{OECD} = 3.28 Rber = 2.52	4	1.72	0.20

Crop	Region/ Indoor (a)	Residue levels observed in the supervised residue trials relevant to the supported GAPs (mg/kg)	Recommendations/comments (OECD calculations)	MRL proposals (mg/kg)	HR (mg/kg) (b)	STMR (mg/kg) (c)
Oats grain	NEU	0.09; 0.39; 0.45; 0.53; 0.55; 0.73; 0.75; 0.94; 1.00; 1.16; 1.50	Rmax = 2.88 Direct extrapolation from barley grain. MRL _{OECD} = 2.32 Rber = 2.0 Rmax = 1.85	3	1.50	0.73
	SEU	-	No data available.	-	-	-
Wheat and rye grain	NEU	0.08; 0.33; 0.53; 0.56; 0.59; 0.61; 0.84; 1.10; 1.67; 1.82	Trials on wheat compliant with GAP (EFSA, 2013; France, 2015). Extrapolation to rye is possible. MRL _{OECD} = 3.06 Rber = 2.49 Rmax = 2.45	3	1.82	0.60
	SEU	0.19; 0.20; 0.23; 0.30; 0.58; 0.75; 0.76	Trials on wheat compliant with GAP (France, 2015). Not authorised use for rye in southern Europe. MRL _{OECD} = 1.46 Rber = 1.50 Rmax = 1.31	1.5	0.76	0.30
Barley straw	NEU	1.1; 1.2; 2.1; 2.3; 2.3; 2.34; 2.34; 2.5; 3.8; 4.6; 5.9	Trials on barley compliant with GAP (EFSA, 2008; France, 2015). MRL _{OECD} = 8.54 Rber = 7.60 Rmax = 6.83	9	5.90	2.34
	SEU	0.46; 0.51; 1.0; 1.83; 1.99; 3.26; 3.35	Trials on barley compliant with GAP authorised on barley (France, 2015). MRL _{OECD} = 6.58 Rber = 6.52 Rmax = 5.86	7	3.35	1.83

Crop	Region/ Indoor (a)	Residue levels observed in the supervised residue trials relevant to the supported GAPs (mg/kg)	Recommendations/comments (OECD calculations)	MRL proposals (mg/kg)	HR (mg/kg) (b)	STMR (mg/kg) (c)
Oats straw	NEU	1.1; 1.2; 2.1; 2.3; 2.3; 2.5; 3.8; 4.6; 5.9; 2.34; 2.34	Direct extrapolation from barley straw. MRL _{OECD} = 8.54 Rber = 7.60 Rmax = 6.83	9	5.90	2.34
	SEU	-	No data available.	-	-	-
Wheat and rye straw	NEU	2.64; 15.3; 22.9; 26.0; 28.3; 39.3; 45.0; 45.7; 50.1	Trials on wheat compliant with GAP (EFSA, 2013; France, 2015). MRL _{OECD} = 93.7 Rber = 90.7 Rmax = 78.4	100	50.1	28.3
	SEU	1.11; 1.79; 2.77; 3.92; 7.29; 7.52; 7.79	Trials on wheat compliant with GAP (France, 2015). Not authorised use for rye in southern Europe. MRL _{OECD} = 16.1 Rber = 15.0 Rmax = 14.4	20	7.79	3.92

* Indicates that the MRL is proposed at the limit of quantification.

Rber : calculated figure for the proposed maximum level; Rmax: maximum residue value

(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): Highest residue.

(c): Supervised trials median residue.

B.1.2.2. Residues in succeeding crops

Confined rotational crop study
(quantitative aspect)

Mepiquat remain levels remain <0.01 mg/kg in all edible commodities investigated. Therefore, significant levels of mepiquat are not expected in rotational crops.

Field rotational crop study

Field rotational crop studies were not required and not reported.

B.1.2.3. Processing factors

Processed commodity	Number of studies ^(a)	Processing Factor (PF)	
		Individual values	Median PF
Robust processing factors (sufficiently supported by data)			
Rape seed, crude oil ^(b)	4	0.01; 0.02; 0.02; 0.06	0.02
Rape seed, refined oil ^(b)	4	0.01; 0.01; 0.01; 0.02	0.01
Rape seed, meal/press cake ^(b)	4	0.98; 1.39; 1.72; 2.24	1.60
Barley, brewing malt ^(c)	4	0.93; 1.14; 1.3; 1.0	1.07
Barley, beer ^(c)	4	0.18; 0.17; 0.19; 0.30	0.18
Barley, pot/pearl ^(c)	4	0.29; 0.71; 0.90; 0.92	0.81
Barley, bran ^(c)	4	2.95; 3.24; 3.68; 4.87	3.46
Wheat, whole-meal flour ^(c)	4	0.09; 0.85; 1.02; 1.38	0.94
Wheat (and rye), whole-meal bread ^(c)	4	0.07; 0.62; 0.86; 0.95	0.74
Wheat (and rye), white flour ^(c)	4	0.14; 0.16; 0.18; 0.26	0.17
Wheat (and rye), bran ^(c)	4	2.95; 3.24; 3.68; 4.87	3.46

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

(b): Source: France, 2015

(c): Source: EFSA, 2013

B.2. Residues in livestock

	Median dietary burden (mg/kg bw per day)	Maximum dietary burden (mg/kg bw per day)	Highest contributing commodity ^(a)	Max dietary burden (mg/kg DM)	Trigger exceeded (Y/N)
Dairy ruminants	0.28	0.47	Wheat straw	12.9	Y
Meat ruminants	0.76	1.30	Wheat straw	30.2	Y
Poultry	0.05	0.05	Barley grain	0.83	Y
Pigs	0.05	0.05	Barley grain	1.14	Y

DM: dry matter; N: no; Y: yes

(a): Calculated for the maximum dietary burden

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/day)	Duration (days)	N rate/comment
	Laying hen	18	6	360 N
	Lactating Goat	19	5	15 N/meat ruminants 40 N/dairy ruminants
In the poultry study, the administrated dose was expressed in mg/kg feed (250 mg/kg feed). EFSA derived a theoretical administrated dose, assuming a body weight of 1.9 kg and a daily intake of 0.14 kg of feed. Source: United Kingdom, 2005				

N: N dose rate

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

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

Metabolism in rat and ruminant similar (Yes/No)

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-hydroxymepiquat and their salts, expressed as mepiquat chloride

Conversion factor (monitoring to risk assessment)

1.7 (ruminant liver)
1 (all other livestock commodities)

Fat soluble residues (Yes/No)

No

Methods of analysis for monitoring of residues (analytical technique, crop groups, 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).

B.2.1.2. Stability of residues in livestock

Animal products (available studies)	Animal	Commodity	T (°C)	Stability (Months/years)
Mepiquat chloride				
	Cow	Tissues (muscle, fat, liver, kidney)	-18	26 months
	Cow	Milk	-18	26 months
	Hen	Tissues (muscle)	-18	26 months
	Hen	Egg	-18	26 months
4-hydroxy-mepiquat				
	Cow	Tissues (liver)	-18	28 months
	Cow	Milk	-18	28 months
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 products, this is deemed sufficient. Source: EFSA, 2008				

B.2.2. Magnitude of residues in livestock

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

Ruminants Closest feeding level ^(a) 2.09 mg/kg bw/day 1.7 N rate (beef cattle) 4.5 N rate (dairy cattle)	Commodity	Residues at closest feeding level ^(b)		Estimated value at 1N		MRL (mg/kg)	CF ^(e)
		Mean (mg/kg)	Highest (mg/kg)	STMR _{Mo} (mg/kg) ^(c)	HR _{Mo} (mg/kg) ^(d)		
	Muscle	0.10	0.12	0.06	0.09	0.09	1
	Fat	0.05	0.05	0.05	0.05	0.06	1
	Liver	0.63	0.73	0.24	0.48	0.50	1.7
	Kidney	0.93	1.2	0.30	0.71	0.80	1
	Milk ^(f)	0.05	n.a.	<0.05	0.05	0.06	1
Poultry	Based on the metabolism study, it is concluded that residue levels in all relevant tissues remain below the enforcement LOQ.						
Pig ^(g) Closest feeding level ^(a) 0.42 mg/kg bw/day 9.2 N rate	Commodity	Residues at closest feeding level ^(b)		Estimated value at 1N		MRL (mg/kg)	CF ^(e)
		Mean (mg/kg)	Highest (mg/kg)	STMR _{Mo} (mg/kg) ^(c)	HR _{Mo} (mg/kg) ^(d)		
	Muscle	<0.05	<0.05	<0.05	<0.05	0.05*	1
	Fat	<0.05	<0.05	<0.05	<0.05	0.05*	1
	Liver	0.14	0.19	<0.05	<0.05	0.05*	1.7
	Kidney	0.15	0.20	<0.05	<0.05	0.05*	1

* Indicates that the MRL is proposed at the limit of quantification.

n.a. not applicable

STMR: supervised trials median residue; HR: highest residue; CF: for enforcement residue definition to risk assessment residue definition

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

(b): Results of the feeding study were recalculated to be expressed as mepiquat chloride using a molecular weight conversion factor of 1.31.

(c): Median residue level according to the residue definition for monitoring recalculated at the 1N rate for the median dietary burden.

(d): Highest residue level for tissues and mean residue level for milk, all according to the residue definition for monitoring, recalculated at the 1N rate for the maximum dietary burden.

(e): Conversion factor for risk assessment derived from the goat metabolism study (significant levels of 4-hydroxy-mepiquat were found in ruminant liver only).

(f): Only the milk samples collected from day 24 were considered (maximum values).

(g): Since extrapolation from ruminants to pigs is acceptable, results of the livestock feeding study on ruminants were relied upon to derive the MRL and risk assessment values in pigs.

B.3. Consumer risk assessment

ADI

Highest IEDI, according to EFSA PRIMo

Assumptions made for the calculations

0.2 mg/kg bw per day (EFSA, 2008)
6.6 % ADI (WHO Cluster diet B)
The calculation is based on the median residue levels in the raw agricultural commodities. For those commodities where data were insufficient to derive an MRL, EFSA considered the existing EU MRL for an indicative calculation. The contributions of commodities where no GAP was reported in the framework of this review were not included in the calculation.

ARfD

Highest IESTI, according to EFSA PRIMo

Assumptions made for the calculations

0.3 mg/kg bw (EFSA, 2008)
10.3 % ARfD (sunflower seed)
The calculation is based on the highest residue levels in the raw agricultural commodities. For those commodities where data were insufficient to derive an MRL, EFSA considered the existing EU MRL for an indicative calculation.

B.4. Proposed MRLs

Code number	Commodity	Existing EU MRL (mg/kg)	Outcome of the review	
			MRL (mg/kg)	Comment
Enforcement residue definition (existing): mepiquat				
Enforcement residue definition (proposed): sum of mepiquat and its salts, expressed as mepiquat chloride				
401010	Linseed	0.05*	0.05*	Further consideration needed ^(a)
401050	Sunflower seed	10	10	Further consideration needed ^(a)
401060	Rape seed	3	4	Further consideration needed ^(b)
500010	Barley grain	3	4	Recommended ^(c)
500050	Oats grain	2	3	Recommended ^(c)
500070	Rye grain	3	3	Recommended ^(c)
500090	Wheat grain	3	3	Recommended ^(c)
1011010	Swine muscle	0.05*	0.05*	Recommended ^(c)
1011020	Swine fat (free of lean meat)	0.05*	0.05*	Recommended ^(c)
1011030	Swine liver	0.05*	0.05*	Recommended ^(c)
1011040	Swine kidney	0.05*	0.05*	Recommended ^(c)
1012010	Bovine muscle	0.08	0.09	Recommended ^(c)
1012020	Bovine fat	0.05*	0.06	Recommended ^(c)
1012030	Bovine liver	0.4	0.5	Recommended ^(c)
1012040	Bovine kidney	0.6	0.8	Recommended ^(c)
1013010	Sheep muscle	0.08	0.09	Recommended ^(c)
1013020	Sheep fat	0.05*	0.06	Recommended ^(c)
1013030	Sheep liver	0.4	0.5	Recommended ^(c)
1013040	Sheep kidney	0.6	0.8	Recommended ^(c)
1014010	Goat muscle	0.08	0.09	Recommended ^(c)
1014020	Goat fat	0.05*	0.06	Recommended ^(c)
1014030	Goat liver	0.4	0.5	Recommended ^(c)
1014040	Goat kidney	0.6	0.8	Recommended ^(c)
1016010	Poultry muscle	0.05*	0.05*	Recommended ^(c)
1016020	Poultry fat	0.05*	0.05*	Recommended ^(c)
1016030	Poultry liver	0.05*	0.05*	Recommended ^(c)
1020010	Cattle milk	0.1	0.06	Recommended ^(c)
1020020	Sheep milk	0.05*	0.06	Recommended ^(c)
1020030	Goat milk	0.05*	0.06	Recommended ^(c)
1030000	Birds' eggs	0.05*	0.05*	Recommended ^(c)
-	Other commodities of plant and animal origin	-	-	Further consideration needed ^(d)

(*): Indicates that the MRL is set at the limit of quantification.

(a): GAP evaluated at EU level is not supported by data but no risk to consumers was identified for the existing EU MRL; no CXL is available (combination C-I in Appendix D).

(b): Tentative MRL is derived from a GAP evaluated at EU level, which is not fully supported by data but for which no risk to consumers was identified; no CXL is available (combination E-I in Appendix D).

(c): MRL is derived from a GAP evaluated at EU level, which is fully supported by data and for which no risk to consumers is identified; no CXL is available (combination G-I in Appendix D).

(d): There are no relevant authorisations or import tolerances reported at EU level; no CXL is available. Either a specific LOQ or the default MRL of 0.01 mg/kg may be considered (combination A-I in Appendix D).

Appendix C – Input values for the exposure calculations

C.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 residue definition : sum of mepiquat and its salts, expressed as mepiquat chloride				
Rapeseed, meal	2	STMR x PF	2	STMR x PF
Wheat and rye grain	0.6	STMR	0.6	STMR
Barley and oat grain	0.7	STMR	0.7	STMR
Wheat and rye bran	2.1	STMR x PF	2.1	STMR x PF
Wheat and rye straw	28.3	STMR	50.1	HR
Barley and oat straw	2.3	STMR	5.9	HR

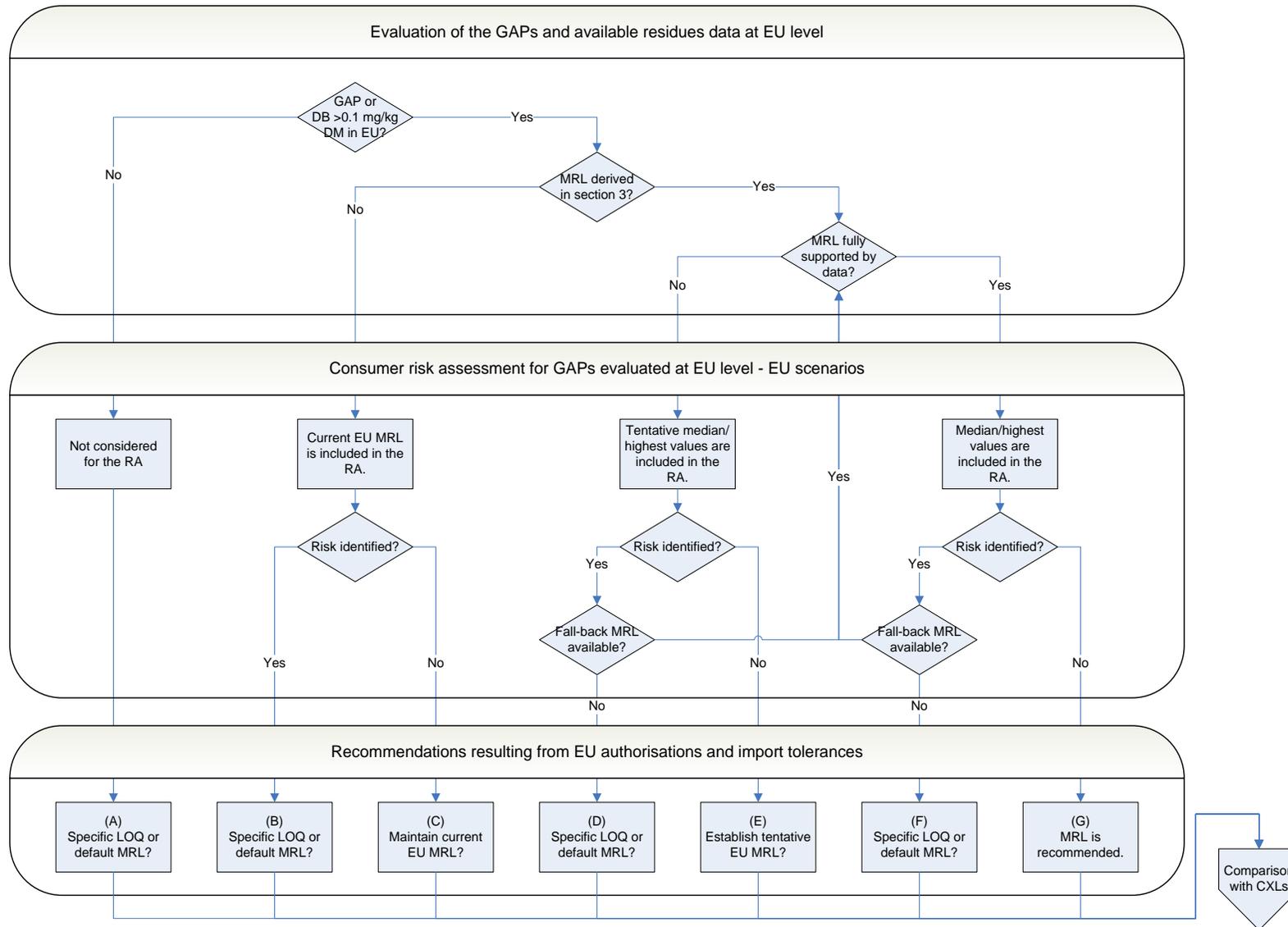
STMR: supervised trials median residue; HR: highest residue; PF: processing factor

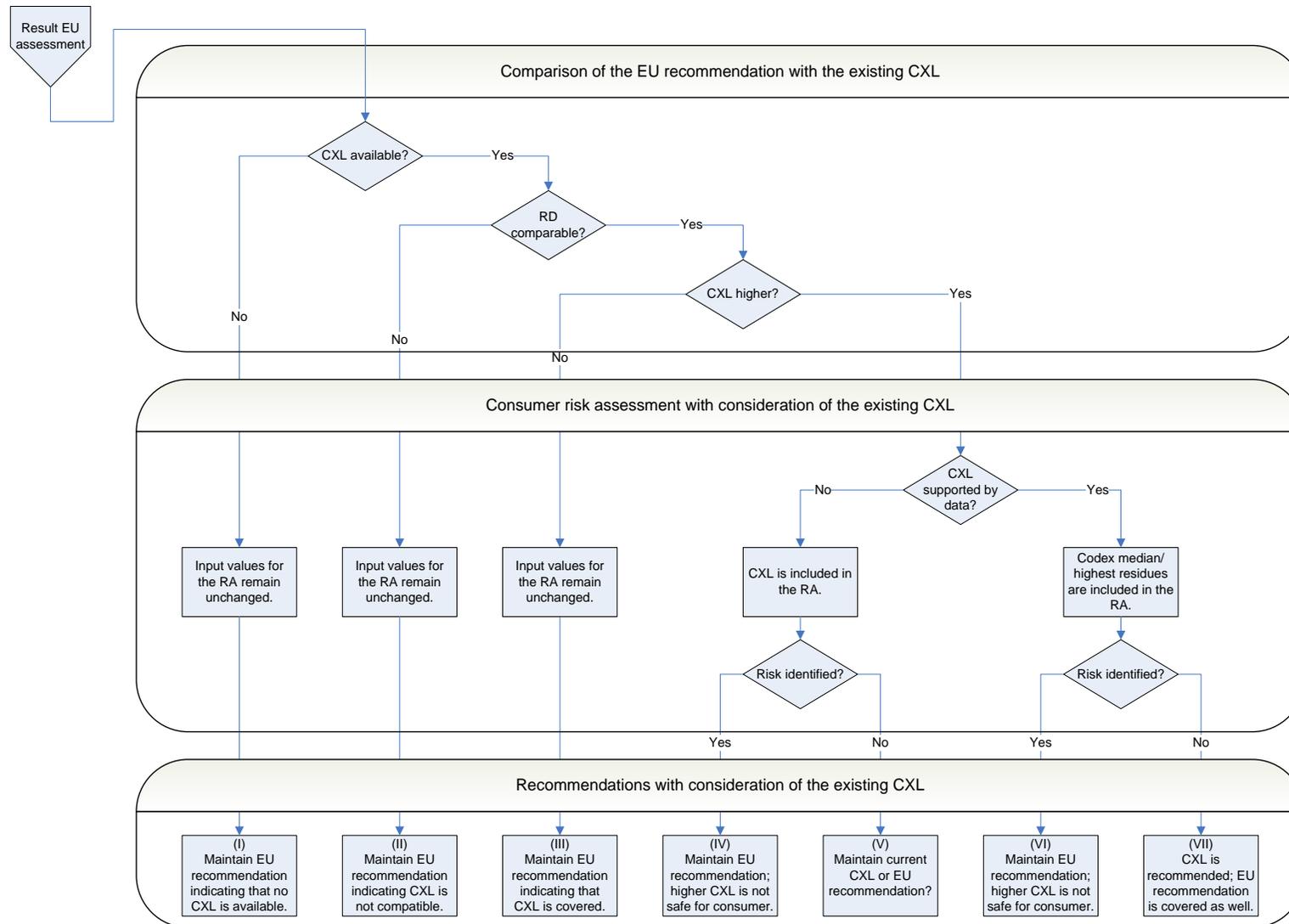
C.2. Consumer risk assessment

Commodity	Chronic risk assessment		Acute risk assessment	
	Input value (mg/kg)	Comment	Input value (mg/kg)	Comment
Risk assessment residue definition 1: sum of mepiquat and its salts, expressed as mepiquat chloride				
Linseed	0.05*	EU MRL	0.05*	EU MRL
Sunflower seed	10	EU MRL	10	EU MRL
Rape seed	1.3	STMR (tentative)	1.9	HR (tentative)
Barley grain	0.7	STMR	1.7	HR
Oats grain	0.7	STMR	1.5	HR
Wheat and rye grain	0.6	STMR	1.8	HR
Risk assessment residue definition 2: sum of mepiquat, 4-hydroxymepiquat and their salts, expressed as mepiquat chloride				
Swine meat	0.05*	0.8 x STMR muscle + 0.2 x STMR fat	0.05*	0.8 x HR muscle + 0.2 x HR fat
Swine fat	0.05*	STMR	0.05*	HR
Swine liver	0.09	STMR _{MO} x CF	0.09	HR _{MO} x CF
Swine kidney	0.05*	STMR	0.05*	HR
Ruminant meat	0.06	0.8 x STMR muscle + 0.2 x STMR fat	0.09	0.8 x HR muscle + 0.2 x HR fat
Ruminant fat	0.05	STMR	0.05	HR
Ruminant liver	0.41	STMR _{MO} x CF	0.81	HR _{MO} x CF
Ruminant kidney	0.30	STMR	0.71	HR
Poultry meat	0.05*	0.9 x STMR muscle + 0.1 x STMR fat	0.05*	0.9 x HR muscle + 0.1 x HR fat
Poultry fat	0.05*	STMR	0.05*	HR
Poultry liver	0.05*	STMR	0.05*	HR
Ruminant milk	0.05*	STMR	0.05	HR
Birds' eggs	0.05*	STMR	0.05*	HR

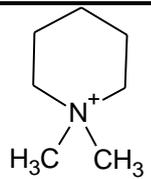
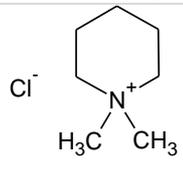
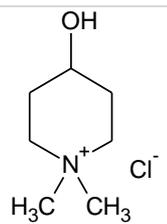
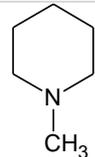
* Indicates that the input value is proposed at the limit of quantification.

Appendix D – Decision tree for deriving MRL recommendations





Appendix E – Used compound code(s)

Code/trivial name	Chemical name/SMILES notation ^(a)	Structural formula ^(a)
mepiquat	1,1-dimethylpiperidinium <chem>C[N+](C)CCCC1</chem>	
mepiquat chloride	1,1-dimethylpiperidinium chloride <chem>[Cl-].C[N+](C)CCCC1</chem>	
4-hydroxy mepiquat-chloride	4-hydroxy-1,1-dimethylpiperidinium chloride <chem>[Cl-].C[N+](C)CCC(O)CC1</chem>	
methylpiperidine	1-methylpiperidine <chem>CN1CCCC1</chem>	

(a): (ACD/ChemSketch, Advanced Chemistry Development, Inc., ACD/Labs Release: 12.00 Product version: 12.00 (Build 29305, 25 Nov 2008).