REASONED OPINION

Reasoned opinion on the review of the existing maximum residue levels (MRLs) for milbemectin according to Article 12 of Regulation (EC) No 396/2005[1]

European Food Safety Authority[2, 3]

European Food Safety Authority (EFSA), Parma, Italy

SUMMARY

Milbemectin was included in Annex I to Directive 91/414/EEC on 01 December 2005, which is before the entry into force of Regulation (EC) No 396/2005 on 02 September 2008. EFSA is therefore required to provide a reasoned opinion on the review of the existing MRLs for that active substance in compliance with Article 12(2) of afore mentioned regulation. In order to collect the relevant pesticide residues data, EFSA asked The Netherlands, as the designated rapporteur Member State (RMS), to complete the Pesticide Residues Overview File (PROFile). The requested information was submitted to EFSA on 23 March 2009 and, after having considered several comments made by EFSA, the RMS provided on 20 November 2009 a revised PROFile.

Based on the conclusions derived in the framework of Directive 91/414/EEC and the additional information provided by the RMS, EFSA issued on 26 September 2011 a draft reasoned opinion that was circulated to Member State experts for consultation. Comments received by 02 December 2011were considered for finalisation of this reasoned opinion. The following conclusions are derived.

The toxicological profile of milbemectin was evaluated in the framework of Directive 91/414/EEC, which resulted in an ADI of 0.03 mg/kg bw/d and an ARfD of 0.03 mg/kg bw. Both toxicological reference values were established for milbemycin A_4 and milbemycin A_3.

Primary crop metabolism of milbemectin was investigated following a foliar application in several fruits (apple, strawberry and orange) at maturity, hereby covering only one crop group. Metabolic patterns in the different studies were shown to be similar and the relevant residue for enforcement and risk assessment in fruits could be defined as sum of milbemycin A_4 and milbemycin A_3, expressed as milbemectin. There is no metabolism study to cover the use on hops. However, as metabolism were also investigated in leaves, and as only the fruit parts of hops (cones) are consumed, the same definition of residue for enforcement and risk assessment can also apply on hops and a supplementary metabolism study is only considered desirable. If in the future, milbemectin would be supported for use on other leafy vegetables, a metabolism study would become necessary. Validated analytical

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[2] Correspondence: pesticides.mrl@efsa.europa.eu

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methods for enforcement of this residue definition are available with an LOQ of 0.02 mg/kg in high water content (apples, pears) and acidic (oranges, strawberries) commodities, and with an LOQ of 0.2 mg/kg in hops.

Regarding the magnitude of residues in all crops reported by the RMS, a sufficient number of supervised residues trials is considered available for all the GAPs reported by the RMS, which allowed EFSA to estimate the expected residue concentrations in the relevant plant commodities and to derive appropriate MRLs.

As residues of milbemectin are all below 0.1 mg/kg and contribution of these residues to chronic consumer exposure is generally low, investigating the effect of industrial and/or household processing was not necessary. Studies investigating the magnitude of residues in some processed products were submitted but processing factors could not be derived for enforcement because residue levels were below the LOQ in the raw agricultural commodities.

Occurrence of milbemectin residues in rotational crops was not investigated during the peer review. Strawberries may be grown in rotation with other crops. As it was demonstrated in several degradation studies that milbemectin is persistent in soil and that DT_{90} values exceed the trigger value of 100 days, a detailed assessment of the nature and magnitude of milbemectin residues is necessary and a rotational crop study is therefore required.

Based on the uses reported by the RMS, no significant intakes were calculated for any group of livestock, further investigation of residues as well as the setting of MRLs in commodities of animal origin is not deemed necessary.

Both chronic and acute consumer exposure resulting from the uses supported in the framework of this review was calculated using revision 2 of the EFSA PRIMo. The highest chronic exposure represented 0.9 % of ADI (German child) and the highest acute exposure amounted to 6.5 % of the ARfD (apple).

Based on the above assessment, EFSA does not recommend inclusion of this active substance in Annex IV to Regulation (EC) No 396/2005. MRL recommendations were derived in compliance with the decision tree reported in Appendix D (see table below for a summary). All MRL values listed in the table are sufficiently supported by data and therefore proposed for inclusion in Annex II to the Regulation.

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

- 8 residue trials complying with the Swedish GAP on pome fruit;
- a rotational crop study investigating the nature and the magnitude of the residue.

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. When granting authorisations on strawberries, Member States are also recommended to consider the need of defining restrictions to avoid the occurrence of milbemectin in succeeding crops.

Minor deficiencies were also identified in the assessment but these deficiencies are not expected to impact either on the validity of the ‘Recommended’ MRLs or on the national authorisations. The following data are therefore considered desirable but not essential:

- an additional metabolism study to support the use on hops.

Code number	Commodity	Existing EU MRL (mg/kg)	Outcome of the review	
			MRL (mg/kg)	Comment
Sum of milbemycin A_4 and milbemycin A_3, expressed as milbemectin				
130000	Pome fruits	0.05*	0.02*	Recommended[(a)]
152000	Strawberries	0.05*	0.02*	Recommended[(a)]
700000	Hops	0.1	0.2*	Recommended[(a)]
-	Other products of plant or animal origin	See appendix C	-	Further consideration needed [(b)]

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

KEY WORDS

Milbemectin, milbemycin, MRL review, Regulation (EC) No 396/2005, consumer risk assessment, insecticide, acaricide.

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BACKGROUND

Regulation (EC) No 396/2005[4] establishes the rules governing the setting as well as the review of pesticide MRLs at European level. Article 12(2) of that regulation stipulates that EFSA shall provide by 01 September 2009 a reasoned opinion on the review of the existing MRLs for all active substances included in Annex I to Directive 91/414/EEC[5] before 02 September 2008. As milbemectine was included in Annex I to the above mentioned directive on 01 December 2005, EFSA initiated the review of all existing MRLs for that active substance and a task with the reference number EFSA-Q-2008-594 was included in the EFSA Register of Questions.

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 on the pesticide residues data that have been considered for the setting of the existing MRLs, EFSA developed the Pesticide Residue 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 Netherlands, the designated rapporteur Member State (RMS) in the framework of Directive 91/414/EEC, was asked to complete the PROFile for milbemectin. The requested information was submitted to EFSA on 23 March 2009 and subsequently checked for completeness. On 20 November 2009, after having clarified some issues with EFSA, the RMS provided a revised PROFile.

A draft reasoned opinion was issued by EFSA on 26 September 2011 and submitted to Member States (MS) for commenting. All MS comments received by 02 December 2011 were considered by EFSA for finalization of the reasoned opinion.

[4] Commission Regulation (EC) No 396/2005 of 23 February 2005. OJ L 70, 16.3.2005, p. 1-16.
[5] Council Directive 91/414/EEC of 15 July 1991, OJ L 230, 19.8.1991, p. 1-32.

TERMS OF REFERENCE

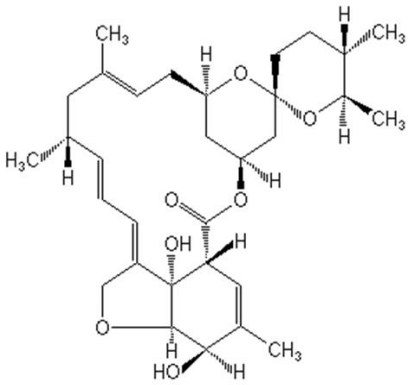
According to Article 12 of Regulation (EC) No 396/2005, EFSA shall provide a reasoned opinion on:

- 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.

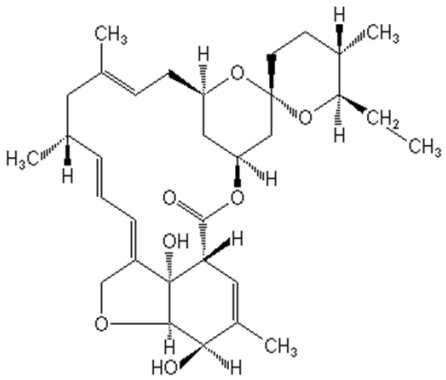
THE ACTIVE SUBSTANCE AND ITS USE PATTERN

Milbemectin, mixture of milbemycin A_3 and milbemycin A_4 (in a ratio of 30:70), is the ISO common name for:

- milbemycin A_3 : (10E,14E,16E,22Z)-(1R,4S,5'S,6R,6'R,8R,13R,20R,21R,24S)-21,24-dihydroxy-5',6',11,13,22-pentamethyl-3,7,19-trioxatetracyclo[15.6.1.1$^{4.8}$.0^{20,24}]pentacosa-10,14,16,22-tetraene-6-spiro-2'-tetrahydropyran-2-one (IUPAC)



- milbemycin A_4 : (10E,14E,16E,22Z)-(1R,4S,5'S,6R,6'R,8R,13R,20R,21R,24S)-6'-ethyl-21,24-dihydroxy-5',11,13,22-tetramethyl-3,7,19-trioxatetracyclo[15.6.1.1$^{4.8}$0^{20,24}]pentacosa-10,14,16,22-tetraene-6-spiro-2'-tetrahydropyran-2-one (IUPAC).



Milbemectin belongs to the group of biopesticide compounds which are used as insecticide and acaricide. It is produced by a fermentation process of Streptomyces in which the resulting product contains both milbmycin A_3 and A_4. Milbemectine is used against mites, aphids, whiteflies,

leafminers and thrips. The mode of action of milbemectin occurs through opening of the chloride channel of the synapse in the nervous system by direct interaction with the GABA-Cl-ion channel complex. It acts in the central nervous system and the neuromuscular junctions causing death of the insects by suppression of the nervous system.

Milbemectin was evaluated in the framework of Directive 91/414/EEC with The Netherlands being the designated rapporteur Member State (RMS). The representative uses supported for the peer review process was two outdoor treatment of apples at a maximum rate of 0.019 kg a.s./ha with a PHI of 14 days and up to ten outdoor treatments on ornementals at a rate of 0.028 kg a.s./ha, both in northern and southern Europe. Following the peer review, a decision on inclusion of the active substance in Annex I to Directive 91/414/EEC was published by means of Commission Directive 2005/58/EC[6], entering into force on 01 December 2005. According to Regulation (EU) No 540/2011[7], milbemectin is deemed to have been approved under Regulation (EC) No 1107/2009[8]. This approval is restricted to uses as acaricide and insecticide only. As EFSA was not yet involved in the peer review of milbemectin, a conclusion of EFSA on this active substance is not available.

The EU MRLs for milbemectin are established in Annexes II and IIIB of Regulation (EC) No 396/2005. All existing EU MRLs, which are established for the sum of milbemycin A_4 and its 8-9Z-isomer, expressed as milbemectin, are summarized in Appendix C to this document. CXLs for milbemectin are not available.

For the purpose of this MRL review, the critical uses of milbemectin currently authorized within the EU, have been collected by the RMS and reported in the PROFile. Additional GAPs were also reported during the Member States consultation (see Appendix A). According to the reported GAPs, milbemectin is applied by foliar spraying under outdoor conditions in pome fruits and strawberries in northern and southern Europe and in hops in northern Europe, and in strawberries under indoor conditions. The RMS did not report any use authorised in third countries that might have a significant impact on international trade.

ASSESSMENT

EFSA bases its assessment on the PROFile submitted by the RMS, the Draft Assessment Report (DAR) and its addenda prepared under Council Directive 91/414/EEC (The Netherlands, 2002, 2003a, 2003b, 2004, 2005) as well as the Review Report on milbemectin (EC, 2005), and the evaluation reports submitted during the Member States consultation (Germany, 2011, 2012). The assessment is performed in accordance with the legal provisions of the Uniform Principles for the Evaluation of the Authorization of Plant Protection Products adopted by Commission Regulation (EU) No 546/2011[9] and the currently applicable guidance documents relevant for the consumer risk assessment of pesticide residues (EC, 1996, 1997a, 1997b, 1997c, 1997d, 1997e, 1997f, 1997g, 2000, 2010a, 2010b, 2011).

1. Methods of analysis

1.1. Methods for enforcement of residues in food of plant origin

During the peer review under Directive 91/414/EEC, an analytical method using HPLC with fluorescence detection was provided; this method is not considered validated due to an inacceptable

[6]Commission Directive 2005/58/EC of 21 September 2005, OJ L 246, 22.9.2005, p. 17-19.
[7] Regulation (EU) No 540/2011 of 25 May 2011, OJ L 153, 11.6.2011, p. 1-186.
[8] Regulation (EC) No 1107/2009 of 21 October 2009, OJ 309, 24.11.2009, p. 1–50.
[9] Regulation (EU) No 546/2011 of 10 June 2011. OJ L 155, 11.06.2011, p. 127-175.

workload (separation of photoisomers by normal phase HPLC) and absence of an acceptable ILV. However, an analytical method using HPLC-MS/MS (inverse phase) was also evaluated during the peer review and validated for determination of milbemycin A_4 and milbemycin A_3 in plant matrices. Considering that milbemycin A_3 and milbemycin A_4 have similar chemical structure, this method can be considered as validated for both milbemycins. The combined LOQ for the sum of milbemycin A_4 and milbemycin A_3 amounts to 0.02 mg/kg in high water content (apples, pears) and acidic (oranges, strawberries) commodities (The Netherlands, 2003a, 2004, 2005).

The multi-residue QuEChERS method in combination with HPLC-MS/MS is also available to dose the sum of milbemycin A_4 and milbemycin A_3 with an LOQ of 0.1 mg/kg for high water content, dry and acidic commodities (CEN, 2008). Nevertheless, the number of fortification level and the number of labs are too low to consider this multi-residue method as sufficiently validated.

Table 1-1: Recovery data for the analysis of the sum of milbemycin A_4 and milbemycin A_3 in different crop groups using the QuEChERS method in combination with HPLC-MS/MS (EURL, 2011)

Commodity group	Spiking levels (mg/kg)		Recoveries			No of labs
	Min.	Max.	Mean (%)	RSD (%)	n	
Acidic	0.1	0.1	99	3	5	1
Dry (cereals, pulses)	0.1	0.1	102	12	5	1
Watery	0.1	0.1	98	6	5	1

During the Member State consultation, Germany provided an analytical method using HPLC-MS/MS for the determination of milbemycin A_3 and milbemycin A_4 in hops. This method was evaluated and validated in hops with an LOQ of 0.2 mg/kg for the sum of milbemycin A_3 and milbemycin A_4 (Germany, 2012).

Hence it is concluded that the sum of milbemycin A_4, milbemycin A_3, expressed as milbemectin can be enforced in food of plant origin with an LOQ of 0.02 mg/kg in high water content and acidic commodities and an LOQ of 0.2 mg/kg in hops.

1.2. Methods for enforcement of residues in food of animal origin

No analytical methods are available for food of animal origin.

2. Mammalian toxicology

The toxicological assessment of milbemycin A_4 and milbemycin A_3 was peer reviewed under Directive 91/414/EEC and toxicological reference values were established by the European Commission (2005). These toxicological reference values are summarized in Table 2-1.

Table 2-1: Overview of the toxicological reference values

	Source	Year	Value	Study relied upon	Safety factor
Milbemycin A_4 and Milbemycin A_3					
ADI	EC	2005	0.03 mg/kg bw/d	12-month oral dog	100
ARfD	EC	2005	0.03 mg/kg bw	90-d and 12-month dog	100

The mutagenicity for the photoisomers 8,9 milbemycin-A_3 and 8,9 milbemycin-A_4 (with an Ames test, a chromosome aberration test and a tk gene mutation test) was evaluated, it was peer reviewed that both photoisomers are not genotoxic (The Netherlands, 2003b, 2005).

3. Residues

3.1. Nature and magnitude of residues in plant

3.1.1. Primary crops

3.1.1.1. Nature of residues

Metabolism of milbemectin was investigated in the framework of the peer review of Directive 91/414/EEC for foliar application on fruits (apple, strawberry and orange) using ^{14}C-milbemycin-A_4 (MA_4) labeled at several places in the molecule (The Netherlands, 2002). One study was also considered to evaluate the absorption of milbemycin-A_4 in eggplant and the translocation of ^{14}C-milbemycin-A_3 (MA_3) and ^{14}C-milbemycin-A_4 in orange (carbon- and tritium-labeled). The characteristics of these studies are summarized in Table 3-1.

In apples at harvest, milbemycin A_4 is extensively degraded into many residues. The parent compound was present at concentrations that did not exceed 0.003 mg eq/kg (7.0 % TRR). The photoisomer 8,9Z-MA_4[10] and an unknown metabolite were not present at concentrations higher than 0.002 mg eq/kg (9.3 % TRR at 1.5N). Furthermore, numerous of radioactive residues were observed at very low levels (< 0.001 mg eq/kg; < 3.4 % TRR). The level of non-extractable residues did not exceed 0.005 mg eq/kg for all the fruit samples at the intended use. The parent compound is the major residue determined whereas at 14 DAT, none of the residues, including the parent compound, exceed levels of 10 % TTR (<0.002 mg eq/kg).

In oranges, metabolism of milbemectin A_4 is extensive over a period of 14 days. In orange peel the main component of the TRR was parent milbemycin A_4 (between 19 and 55 % TRR) and minor amounts (< 0.007 mg eq/kg, 8.5 % TRR) were attributed to the photoisomer 8,9Z-MA_4, 27-keto-MA_4[11] and an unknown metabolite. In orange pulp, total levels of radioactivity were low (≤0.010 mg eq/kg) and no further identification and characterisation was performed.

[10] 8,9-MA_4: 8,9-milbemycin A_4 (see Appendix E)
[11] 27-keto-MA_4: 27-keto-milbemycin A_4 (see Appendix E)

Table 3-1: Summary of available metabolism studies in plants

Group	Crop	Label position	Application and sampling details				
			Method, F or G [(a)]	**Rate (g a.s./ha)**	**No**	**Sampling (DAT)**	**Remarks**
Fruits and fruiting vegetable	**Apple** (Granny Smith)	^{14}C-MA$_4$[b]	Foliar application at maturity	27.2 (1.5N)	1	7 and 14	
				54.4 (2.9N)			
	Strawberry (*Fragaria x Ananassa* 'Tristar')	^{14}C-MA$_4$[b]	Foliar application at maturity (90% or more of fruits were mature); G	21.8	1	1 and 3	
				87.2			
	Orange (*Citrus sinensis*)	^{14}C-M A$_4$[b]	Foliar application at maturity, G	27.2	1	7 and 14	
				54.4			
	Orange (Unshu orange)	5-^{3}H-MA$_3$, 30-^{3}H-MA$_3$, 5-^{3}H-MA$_4$, 26-^{3}H-MA$_4$, 29-^{3}H-MA$_4$, 30-^{3}H-MA$_4$, ^{14}C-MA$_3$[c], ^{14}C-MA$_4$[c]	Locally application on leaves and fruits of a branch	MA$_3$: 0.4ml to leaves (1.2 µg); 0.2 ml to fruit (0.6 µg)	1	1, 3, 6, 15, 30, 60, and 90	Data are considered of limited value, because of methodological shortcomings
				MA$_4$: 0.4ml to leaves (2.8 µg); 0.2 ml to fruit (1.4 µg)			
	Egg plant	30-^{3}H-MA$_4$	Soil application at three leaves stage	0.5 mg eq./kg	1	1, 3, 6, 9 and 30	

(a): Outdoor/field application (F) or glasshouse/protected/indoor application (G)
(b): The label is positioned at several places in the molecule, including the cyclic parts
(b): The position of the label is not indicated

After the application of tritium-labelled milbemycin A$_3$ and milbemycin A$_4$ to orange leaves and fruit, degradation was extensive and a high number of metabolites were formed over a period of 15 days. Minimal translocation from treated leaves to untreated leaves and fruits takes place over a period of 90 days. The absorption of milbemycin A$_4$ in eggplants from the soil is negligible over a course of 30 days.

In strawberries, milbemycin A_4 is not metabolised to a great extent over the course of 3 days. The major radioactive residue was the parent compound (for 44 to 89 % TRR) and other remaining radioactive residues were present at very low levels.

The peer review concluded that the metabolism of milbemycin A_4 was investigated in several fruit crops and only limited study was provided on the distribution and metabolism of milbemycin A_3. As milbemectin is a mixture of milbemycin A_4 and A_3, the metabolism of both milbemycin compounds should normally be investigated. However considering that 1) 70 % of the mixture was milbemycine A_4, that the metabolism of milbemycin A_4 was determined, 2) the residues levels were all below the LOQ, 3) according to the study with milbemycin A_4 and A_3 on orange, the metabolism of milbemycin A_4 and A_3 is expected to be similar and 4) milbemycin A_4 and A_3 are structurally very similar (methyl versus ethyl side chain), no remarkable differences in metabolic pathway of both parent compounds are expected. As parent milbemycin A_4 and the photoisomer 8,9Z-MA_4 were the main components identified in the metabolism studies, the peer review concluded to define the relevant residue for enforcement in fruits as the sum of milbemycin A_4 and its photoisomer 8,9Z-MA_4, expressed as milbemectin.

With the assumption that the toxicity of milbemycin A_3 and its photoisomer are similar to that of milbemycin A_4 and its photoisomer, it was proposed to also include compound milbemycin A_3 and its photoisomer in the residue definition for risk assessment in plant commodities. Milbemectin consisting of 70 % of milbemycin A_4 and 30 % of milbemycin A_3 and since, in all commodities, the residue levels of both compounds including their corresponding photoisomers were below the LOQ of 0.02 mg/kg, a conversion factor of 1.5 was proposed linked to the ratio of milbemycin A_4 and milbemycin A_3.

However EFSA noted that no structural alerts with regard to toxicity have been identified for the photoisomer of milbemectin A_4 and A_3 and the supplying toxicological studies with photoisomer submitted by the notifier demonstrated their non relevance (The Netherlands, 2003b; 2005). In addition, due to the very rapid degradation of the photoisomers in crops, their levels remain very low (<0.002 mg eq/kg). Moreover the analytical method covers milbemycin A_4 and A_3. Therefore, the residue definition for enforcement should include both types of milbemycin. Consequently, the relevant residue for enforcement and risk assessment in fruits is defined as the sum of milbemycin A_4 and milbemycin A_3, expressed as milbemectin. Validated analytical methods for enforcement of the proposed residue definition are available (see also section 1.1).

It is noted that milbemectin is also authorised for use on hops, which is a matrix rather difficult to classify; it belongs to leafy vegetables but only the fruit parts of hops (cones) are normally consumed. Considering that milbemectin is applied before formation of those consumable parts, that metabolism was investigated on fruit and leaves and that residue trials confirm a no residue situation (see section 3.1.1.2), EFSA is of the opinion that the same residue definition for enforcement and risk assessment could apply for hops and a metabolism study should only be considered as desirable. Nevertheless, if in the future, milbemectin would be supported for use on other leafy vegetables, a metabolism study would become necessary.

3.1.1.2. Magnitude of residues

According to the RMS, the active substance milbemectin is authorised for foliar treatment in pome fruits and strawberries in northern and southern Europe, in strawberries under indoor conditions and in hops in northern Europe (see Appendix A). To assess the magnitude of milbemectin residues resulting from these GAPs, EFSA considered all residues trials reported in the PROFile, including residues trials evaluated in the framework of the peer review (The Netherlands, 2002) and additional data submitted during the Member States consultation (Germany, 2011). All available residues trials that, according to the RMS, comply with the authorised GAPs, are summarized in Table 3-2.

The number of residue trials and extrapolations were evaluated according to the European guidelines on comparability, extrapolation, group tolerances and data requirements for setting MRLs (EC, 2011). A sufficient number of trials complying with the GAPs was reported by the RMS for all crops under assessment, except in the following cases:

- Pome fruit: the application rate expressed in g a.s./hL is the only parameter available to compare the different GAPs and residues trials reported by MS. Based on this criterion, the Swedish GAP appears to be the most critical but no residue data are complying with this GAP. Consequently, the GAP reported by Germany and fully supported by data was considered for deriving appropriate MRL and risk assessment values (Germany, 2011). However, 8 residue trials complying with the Swedish GAP are in principle still required.

- Strawberries: no residue trials are available to support the northern and indoor uses. In indoor conditions, the applications are carried out after harvest of the consumable parts of the plant while for the northern use, milbemectin is applied before formation of the consumable parts. Considering that the southern trials were carried out with a much more critical GAP (PHI of 3d) and all available residue levels were below the LOQ, EFSA is of the opinion that residues exceeding the LOQ are anyhow not expected. EFSA considers thus that the statement of the RMS is sufficiently supported by data and further residue trials are not required.

- Hops: the number of residue trials supporting the northern outdoor GAP is not compliant with the data requirements for this crop. However, the reduced number of residue trials is considered acceptable in this case because all results were all below the LOQ and a no residues situation is expected. Further residue trials are therefore not required.

The potential degradation of residues during storage of residue trials samples was also assessed. In the framework of the peer review, storage stability of milbemectin was demonstrated for a period of 12 months at -15°C in commodities with high water (apple and strawberry) and high acid (orange) content (The Netherlands, 2002). According to the RMS, all residue trial samples reported in the PROFile were stored in compliance with the above reported storage conditions. Concerning hops, no storage stability data are available but samples of the reported residue trials were stored frozen for less than one month. Degradation of residues during storage of the trial samples is therefore not expected.

Consequently the available residue data are considered sufficient to derive adequate MRL proposals as well as risk assessment values for all commodities under evaluation (see also Table 3-2).

Table 3-2: Overview of the available residues trials data

Commodity	Region [a]	Outdoor /Indoor	Individual trial results (mg/kg)		Median residue (mg/kg) [b]	Highest residue (mg/kg) [c]	MRL proposal (mg/kg)	Median CF [d]	Comments
			Enforcement (sum of milbemycin A_4 and milbemycin A_3, expressed as milbemectin)	Risk assessment (sum of milbemycin A_4 and milbemycin A_3, expressed as milbemectin)					
Pome fruits	NEU	Outdoor	8 x <0.02	8 x <0.02	0.02	0.02	0.02*	1.00	Combined dataset on apples (7) and pears (1) 1.4 g a.s./hL instead of 1.2 (within 25 % deviation of GAP on apples); extrapolation to all pome fruits possible. SE GAP on apples and pears which is more critical is not supported by data.
	SEU	Outdoor	8 x <0.02	8 x <0.02	0.02	0.02	0.02*	1.00	Combined dataset on apples (6) and pears (2) with 1.4 g a.s./hL instead of 1.2 (within 25 % deviation of GAP on apples); extrapolation to less critical GAP on other pome fruits possible as residues are below LOQ.
Strawberries	NEU	Outdoor	-	-	0.02	0.02	0.02*	1.00	Application before formation of the consumable parts; no residues are expected (see text).
	SEU	Outdoor	8 x <0.02	8 x <0.02	0.02	0.02	0.02*	1.00	Trials compliant with GAP but storage conditions could not be assessed because only summary sheets were available to the RMS.
	EU	Indoor	-	-	0.02	0.02	0.02*	1.00	Application after harvest; no residues are expected (see text).

Commodity	Region (a)	Outdoor /Indoor	Individual trial results (mg/kg)		Median residue (mg/kg) (b)	Highest residue (mg/kg) (c)	MRL proposal (mg/kg)	Median CF (d)	Comments
			Enforcement (sum of milbemycin A_4 and milbemycin A_3, expressed as milbemectin)	Risk assessment (sum of milbemycin A_4 and milbemycin A_3, expressed as milbemectin)					
Hops	NEU	Outdoor	2 x <0.02	2 x <0.02	0.2(e)	0.2(e)	0.2*	1.0	Trials compliant with GAP. 4 other trials available with residue level <LOQ but samples were stored for 25 months (Germany, 2011).

(a): NEU, SEU, EU or Import (country code). In the case of indoor uses there is no necessity to differentiate between NEU and SEU.
(b): Median value of the individual trial results according to the enforcement residue definition.
(c): Highest value of the individual trial results according to the enforcement residue definition.
(d): The median conversion factor for enforcement to risk assessment is obtained by calculating the median of the individual conversion factors for each residues trial.
(e): As the LOQ in the trials is significantly lower than the LOQ for enforcement, median and highest residue values for risk assessment are based on the higher one (worst-case assumption).
(*): Indicates that the MRL is set at the limit of analytical quantification.

3.1.1.3. Effect of industrial processing and/or household preparation

Studies investigating the magnitude of residues in processed commodities are not considered necessary because residues were found to be below the LOQ for all commodities that are likely to be processed. However four residues trials investigating the magnitude of milbemectin residues in sauce and juice of apples were reported by the RMS. According to the RMS, a processing factor of 1 should be proposed because no concentration of the milbemectin was expected (The Netherlands, 2002). EFSA is on the opinion that robust processing factors cannot be derived because residue levels were below the LOQ in this crop. Moreover, the effect of processing on the nature of residues was also not investigated.

Nevertheless, further processing studies are not required in this case as they are not expected to affect the outcome of the risk assessment. If more robust processing factors were to be required by risk managers, in particular for enforcement purposes, additional processing studies would be needed.

3.1.2. Rotational crops

The crops evaluated during the peer review were not considered relevant with regard to the potential occurrence of residues in rotational crops and further investigation of residues in rotational crops was not required. According to the RMS, a rotational crops study is also not required in the framework of this MRL review because strawberries may be grown on the same field for several years. EFSA is however of the opinion that although strawberry plants are kept on the same field for 3-4 years, strawberry plants are afterwards usually rotated with another crop (to avoid occurrence of fungal diseases). During the peer review under Directive 91/414/EEC, it was also demonstrated in several degradation studies that milbemectin is persistent in soil and that DT_{90} values exceed the trigger value of 100 days (The Netherlands, 2002). A detailed assessment of the nature and magnitude of milbemectin residues is therefore necessary and a rotational crop study is therefore still required.

3.2. Nature and magnitude of residues in livestock

Milbemectin is authorised for use on crops (pome fruits) that might be fed to livestock. The median and maximum dietary burdens were therefore calculated for different groups of livestock using the agreed European methodology (EC, 1996).The input values for the only relevant commodity have been selected according to the recommendations of JMPR (FAO, 2009) and are summarized in Table 3-3. As the residue level remains well below the LOQ (based on metabolism study and residues trials), no concentration of residues in apple pomace is expected. The default process factor of 2.5 was therefore not included.

Table 3-3: Input values for the dietary burden calculation

Commodity	Median dietary burden		Maximum dietary burden	
	Input value (mg/kg)	Comment	Input value (mg/kg)	Comment
Sum of milbemycin A_4 and milbemycin A_3, expressed as milbemectin				
Apple pomace	0.02	Median residue (=LOQ)	0.02	Median residue (=LOQ)

The results of the calculations are reported in Table 3-4. Since the calculated dietary burdens for all groups of livestock were found to be below the trigger value of 0.1 mg/kg DM, further investigation of residues as well as the setting of MRLs in commodities of animal origin is not necessary.

Table 3-4: Results of the dietary burden calculation

	Maximum dietary burden (mg/kg bw/d)	Median dietary burden (mg/kg bw/d)	Highest contributing commodity	Max dietary burden (mg/kg DM)	Trigger exceeded (Y/N)
Sum of milbemycin A_4 and milbemycin A_3, expressed as milbemectin					
Dairy ruminants	0.0003	0.0003	Apple pomace	0.01	N
Meat ruminants	0.0011	0.0011	Apple pomace	0.03	N
Poultry	-	-	Not relevant	-	N
Pigs	-	-	Not relevant	-	N

4. Consumer risk assessment

Chronic and acute exposure calculations for all crops supported in the framework of this review were performed using revision 2 of the EFSA Pesticide Residues Intake Model (PRIMo) (EFSA, 2007). Input values for the intake calculations were derived in compliance with Appendix D and are summarized in Table 4-1. The median residue and highest residue values selected for chronic and acute intake calculations are based on the residue levels in the raw agricultural commodities. The contributions of other commodities, for which no was authorisation was reported in the framework of this review, were not included in the calculation.

Table 4-1: Input values for the consumer risk assessment

Commodity	Chronic risk assessment		Acute risk assessment	
	Input value (mg/kg)	Comment	Input value (mg/kg)	Comment
Sum of milbemycin A_4, and milbemycin A_3, expressed as milbemectin				
Pome fruits	0.02	Median residue (=LOQ)[(a)]	0.02	Highest residue (=LOQ)[(a)]
Strawberries	0.02	Median residue (=LOQ)[(a)]	0.02	Highest residue (=LOQ)[(a)]
Hops (dried)	0.2	Median residue (=LOQ)[(a)]	0.2	Highest residue (=LOQ)[(a)]

(a): At least one relevant GAP reported by the RMS is fully supported by data for this commodity; the risk assessment values derived in section 3 are used for the exposure calculations.

The calculated exposures were compared with the toxicological reference values derived for milbemectin (see Table 2-1); detailed results of the calculations are presented in Appendix B. The highest chronic exposure was calculated for German children, representing 0.9 % of the ADI, and the highest acute exposure was calculated for apples, representing 6.5 % of the ARfD.

Based on the above calculations, EFSA concludes that the use of milbemectin on all crops reported is fully supported by data and acceptable with regard to consumer exposure.

CONCLUSIONS AND RECOMMENDATIONS

CONCLUSIONS

The toxicological profile of milbemectin was evaluated in the framework of Directive 91/414/EEC, which resulted in an ADI of 0.03 mg/kg bw/d and an ARfD of 0.03 mg/kg bw. Both toxicological reference values were established for milbemycin A_4 and milbemycin A_3.

Primary crop metabolism of milbemectin was investigated following a foliar application in several fruits (apple, strawberry and orange) at maturity, hereby covering only one crop group. Metabolic patterns in the different studies were shown to be similar and the relevant residue for enforcement and risk assessment in fruits could be defined as sum of milbemycin A_4 and milbemycin A_3, expressed as milbemectin. There is no metabolism study to cover the use on hops. However, as metabolism were also investigated in leaves, and as only the fruit parts of hops (cones) are consumed, the same definition of residue for enforcement and risk assessment can also apply on hops and a supplementary metabolism study is only considered desirable. If in the future, milbemectin would be supported for use on other leafy vegetables, a metabolism study would become necessary. Validated analytical methods for enforcement of this residue definition are available with an LOQ of 0.02 mg/kg in high water content (apples, pears) and acidic (oranges, strawberries) commodities, and with an LOQ of 0.2 mg/kg in hops.

Regarding the magnitude of residues in all crops reported by the RMS, a sufficient number of supervised residues trials is considered available for all the GAPs reported by the RMS, which allowed EFSA to estimate the expected residue concentrations in the relevant plant commodities and to derive appropriate MRLs.

As residues of milbemectin are all below 0.1 mg/kg and contribution of these residues to chronic consumer exposure is generally low, investigating the effect of industrial and/or household processing was not necessary. Studies investigating the magnitude of residues in some processed products were submitted but processing factors could not be derived for enforcement because residue levels were below the LOQ in the raw agricultural commodities.

Occurrence of milbemectin residues in rotational crops was not investigated during the peer review. Strawberries may be grown in rotation with other crops. As it was demonstrated in several degradation studies that milbemectin is persistent in soil and that DT_{90} values exceed the trigger value of 100 days, a detailed assessment of the nature and magnitude of milbemectin residues is necessary and a rotational crop study is therefore required.

Based on the uses reported by the RMS, no significant intakes were calculated for any group of livestock, further investigation of residues as well as the setting of MRLs in commodities of animal origin is not deemed necessary.

Both chronic and acute consumer exposure resulting from the uses supported in the framework of this review was calculated using revision 2 of the EFSA PRIMo. The highest chronic exposure represented 0.9 % of ADI (German child) and the highest acute exposure amounted to 6.5 % of the ARfD (apple).

RECOMMENDATIONS

Based on the above assessment, EFSA does not recommend inclusion of this active substance in Annex IV to Regulation (EC) No 396/2005. MRL recommendations were derived in compliance with the decision tree reported in Appendix D (see table below for a summary). All MRL values listed in

the table are sufficiently supported by data and therefore proposed for inclusion in Annex II to the Regulation.

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

- 8 residue trials complying with the Swedish GAP on pome fruit;
- a rotational crop study investigating the nature and the magnitude of the residue.

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. When granting authorisations on strawberries, Member States are also recommended to consider the need of defining restrictions to avoid the occurrence of milbemectin in succeeding crops.

Minor deficiencies were also identified in the assessment but these deficiencies are not expected to impact either on the validity of the 'Recommended' MRLs or on the national authorisations. The following data are therefore considered desirable but not essential:

- an additional metabolism study to support the use on hops.

Code number	Commodity	Existing EU MRL (mg/kg)	Outcome of the review	
			MRL (mg/kg)	Comment
Sum of milbemycin A_4 and milbemycin A_3, expressed as milbemectin				
130000	Pome fruits	0.05*	0.02*	Recommended[(a)]
152000	Strawberries	0.05*	0.02*	Recommended[(a)]
700000	Hops	0.1	0.2*	Recommended[(a)]
-	Other products of plant or animal origin	See appendix C	-	Further consideration needed [(b)]

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

DOCUMENTATION PROVIDED TO EFSA

1. Pesticide Residues Overview File (PROFile) on milbemectin prepared by the rapporteur Member State The Netherlands in the framework of Article 12 of Regulation (EC) No 396/2005. Submitted to EFSA on 23 March 2009. Last updated on 20 November 2009.

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APPENDIX A – GOOD AGRICULTURAL PRACTICES (GAPS)

Critical Outdoor GAPs for Northern Europe																				
Crop		Region	Outdoor/ Indoor	Member state or Country	Pests controlled	Formulation			Application							Application rate			PHI or waiting period (days)	Comments (max. 250 charachters)
							Content			Growth stage		Number		Interval (days)						
Common name	Scientific name					Type	Conc.	Unit	Method	From BBCH	Until BBCH	Min.	Max.	Min.	Max.	Min. rate	Max. rate	Rate Unit		
Apples	*Malus domesticus*	NEU	Outdoor	DE	spidermites	EC	9,3	g/L	Foliar treatment - spraying	69	76	1	2	60	60	1,20	1,20	g a.i./hL	14	Rate of 5.8 g a.i./ha per m crown height and a volume of 500L/ha and per m of crown height => 1.2 g a.s./hL. Also authorised in SE at a more critical rate of 2.4-3.5 g a.i./hL, but not supported by data.
Pears	*Pyrus communis*	NEU	Outdoor	DE	spidermites	EC	9,3	g/L	Foliar treatment - spraying	69	76	1	2	60	60	1,20	1,20	g a.i./hL	14	Rate of 5.8 g a.i./ha per m crown height and a volume of 500L/ha and per m of crown height => 1.2 g a.s./hL. Also authorised in SE at a more critical rate of 2.4-3.5 g a.i./hL, but not supported by data.
Quinces	*Cydonia oblonga*	NEU	Outdoor	DE	spidermites	EC	9,3	g/L	Foliar treatment - spraying	69	76	1	2	60	60	1,20	1,20	g a.i./hL	14	Rate of 5.8 g a.i./ha per m crown height and a volume of 500L/ha and per m of crown height => 1.2 g a.s./hL.
Medlar	*Mespilus germanica*	NEU	Outdoor	DE	spidermites	EC	9,3	g/L	Foliar treatment - spraying	69	76	1	2	60	60	1,20	1,20	g a.i./hL	14	Rate of 5.8 g a.i./ha per m crown height and a volume of 500L/ha and per m of crown height => 1.2 g a.s./hL.
Loquat	*Eriobotrya japonica*	NEU	Outdoor	DE	spidermites	EC	9,3	g/L	Foliar treatment - spraying	69	76	1	2	60	60	1,20	1,20	g a.i./hL	14	Rate of 5.8 g a.i./ha per m crown height and a volume of 500L/ha and per m of crown height => 1.2 g a.s./hL.
Strawberries	*Fragaria x ananassa*	NEU	Outdoor	DE	spidermites, strawberry mites	EC	9,3	g/L	Foliar treatment - spraying	61	65	1	2	60		11,60	11,60	g a.i./ha	n.a.	
Hops	*Humulus lupulus*	NEU	Outdoor	DE	spidermites	EC	9,3	g/L	Foliar treatment - spraying	65	85	1	2	60		11,60	11,60	g a.i./ha	21	

Critical Outdoor GAPs for Southern Europe																				
Crop		Region	Outdoor/ Indoor	Member state or Country	Pests controlled	Formulation			Application							Application rate			PHI or waiting period (days)	Comments (max. 250 charachters)
							Content			Growth stage		Number		Interval (days)						
Common name	Scientific name					Type	Conc.	Unit	Method	From BBCH	Until BBCH	Min.	Max.	Min.	Max.	Min. rate	Max. rate	Rate Unit		
Apples	*Malus domesticus*	SEU	Outdoor	FR, IT	mites	EC	9,3	g/L	Foliar treatment - spraying	69	85	1	2	10	21	0,93	1,16	g a.i./hL	14	
Pears	*Pyrus communis*	SEU	Outdoor	SI	mites		9,3	g/L	Foliar treatment - spraying	71	76	1	2			5,80	5,80	g a.i./ha	14	authorisation in crop group "pome fruit". Interval not stated, volume 10-15hL/ha
Quinces	*Cydonia oblonga*	SEU	Outdoor	SI	mites		9,3	g/L	Foliar treatment - spraying	71	76	1	2			5,80	5,80	g a.i./ha	14	authorisation in crop group "pome fruit". Interval not stated, volume 10-15hL/ha
Medlar	*Mespilus germanica*	SEU	Outdoor	SI	mites		9,3	g/L	Foliar treatment - spraying	71	76	1	2			5,80	5,80	g a.i./ha	14	authorisation in crop group "pome fruit". Interval not stated, volume 10-15hL/ha
Loquat	*Eriobotrya japonica*	SEU	Outdoor	SI	mites		9,3	g/L	Foliar treatment - spraying	71	76	1	2			5,80	5,80	g a.i./ha	14	authorisation in crop group "pome fruit". Interval not stated, volume 10-15hL/ha
Strawberries	*Fragaria x ananassa*	SEU	Outdoor	IT	mites	EC	9,3	g/L	Foliar treatment - spraying	60	89	1	2	15	15	4,64	8,37	g a.i./ha	3	

Critical Indoor GAPs for Northern and Southern Europe (incl. post-harvest treatments)																				
Crop		Region	Outdoor/ Indoor	Member state or Country	Pests controlled	Formulation			Application							Application rate			PHI or wiaiting period (days)	Comments (max. 250 charachters)
							Content			Growth stage		Number		Interval (days)						
Common name	Scientific name					Type	Conc.	Unit	Method	From BBCH	Until BBCH	Min.	Max.	Min.	Max.	Min. rate	Max. rate	Rate Unit		
Strawberries	*Fragaria x ananassa*	NEU/SEU	Indoor	SE	spidermites, strawberry mites	EC	9,3	g/L	Foliar treatment - spraying	91	91	1	1			23,25	23,25	g a.i./ha	n.a.	either 1 application of 23.25 g as/ha or 2x 11.625 g as/ha after harvest. Interval for 2 applications not stated.

APPENDIX B – PESTICIDE RESIDUES INTAKE MODEL (PRIMO)

milbemectin			
Status of the active substance:	**Included**	Code no.	
LOQ (mg/kg bw):		proposed LOQ:	
Toxicological end points			
ADI (mg/kg bw/day):	**0.03**	ARfD (mg/kg bw):	**0.03**
Source of ADI:	**COM**	Source of ARfD:	**COM**
Year of evaluation:	**2005**	Year of evaluation:	**2005**

Chronic risk assessment - refined calculations

TMDI (range) in % of ADI minimum - maximum	
No of diets exceeding ADI:	--- 1

Highest calculated TMDI values in % of ADI	MS Diet	Highest contributor to MS diet (in % of ADI)	Commodity / group of commodities	2nd contributor to MS diet (in % of ADI)	Commodity / group of commodities	3rd contributor to MS diet (in % of ADI)	Commodity / group of commodities	pTMRLs at LOQ (in % of ADI)
0.9	DE child	0.8	Apples	0.0	Pears	0.0	Strawberries	
0.5	NL child	0.4	Apples	0.0	Pears	0.0	Strawberries	
0.2	FR toddler	0.2	Apples	0.0	Strawberries	0.0	Pears	
0.2	FR infant	0.2	Apples	0.0	Strawberries	0.0	Pears	
0.2	DK child	0.2	Apples	0.0	Pears	0.0	Strawberries	
0.2	PL general population	0.1	Apples	0.0	Pears	0.0	Strawberries	
0.1	UK Toddler	0.1	Apples	0.0	Strawberries	0.0	Pears	
0.1	LT adult	0.1	Apples	0.0	Pears	0.0	Strawberries	
0.1	UK Infant	0.1	Apples	0.0	Pears	0.0	Strawberries	
0.1	IE adult	0.1	Apples	0.0	Pears	0.0	Strawberries	
0.1	ES child	0.1	Apples	0.0	Pears	0.0	Strawberries	
0.1	SE general population 90th percentile	0.1	Apples	0.0	Pears	0.0	Strawberries	
0.1	WHO Cluster diet B	0.1	Apples	0.0	Pears	0.0	Strawberries	
0.1	PT General population	0.1	Apples	0.0	Pears	0.0	Strawberries	
0.1	NL general	0.1	Apples	0.0	Pears	0.0	Strawberries	
0.1	IT kids/toddler	0.1	Apples	0.0	Pears	0.0	Strawberries	
0.1	ES adult	0.1	Apples	0.0	Pears	0.0	Strawberries	
0.1	WHO cluster diet E	0.1	Apples	0.0	Pears	0.0	Strawberries	
0.1	IT adult	0.1	Apples	0.0	Pears	0.0	Strawberries	
0.1	DK adult	0.1	Apples	0.0	Pears	0.0	Strawberries	
0.1	WHO regional European diet	0.0	Apples	0.0	Pears	0.0	Strawberries	
0.1	WHO Cluster diet F	0.0	Apples	0.0	Pears	0.0	Strawberries	
0.1	WHO cluster diet D	0.0	Apples	0.0	Pears	0.0	Strawberries	
0.1	UK vegetarian	0.0	Apples	0.0	Pears	0.0	Strawberries	
0.0	FR all population	0.0	Apples	0.0	Pears	0.0	Strawberries	
0.0	UK Adult	0.0	Apples	0.0	Pears	0.0	Strawberries	
0.0	FI adult	0.0	Apples	0.0	Strawberries	0.0	Pears	

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

Acute risk assessment /children - refined calculations						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 variabilty factor of 3.

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

Unprocessed commodities

No of commodities for which ARfD/ADI is exceeded (IESTI 1): ---			No of commodities for which ARfD/ADI is exceeded (IESTI 2): ---			No of commodities for which ARfD/ADI is exceeded (IESTI 1): ---			No of commodities for which ARfD/ADI is exceeded (IESTI 2): ---		
IESTI 1	*)	**)	IESTI 2	*)	**)	IESTI 1	*)	**)	IESTI 2	*)	**)
Highest % of ARfD/ADI	Commodities	pTMRL/ threshold MRL (mg/kg)	Highest % of ARfD/ADI	Commodities	pTMRL/ threshold MRL (mg/kg)	Highest % of ARfD/ADI	Commodities	pTMRL/ threshold MRL (mg/kg)	Highest % of ARfD/ADI	Commodities	pTMRL/ threshold MRL (mg/kg)
6.5	Apples	0.02 / -	4.8	Apples	0.02 / -	1.5	Apples	0.02 / -	1.2	Apples	0.02 / -
6.1	Pears	0.02 / -	4.4	Pears	0.02 / -	1.4	Pears	0.02 / -	1.1	Pears	0.02 / -
1.0	Strawberries	0.02 / -	1.0	Strawberries	0.02 / -	0.5	Quinces	0.02 / -	0.4	Quinces	0.02 / -
1.0	Quinces	0.02 / -	0.8	Quinces	0.02 / -	0.4	Medlar	0.02 / -	0.4	Strawberries	0.02 / -
0.8	Medlar	0.02 / -	0.6	Medlar	0.02 / -	0.4	Strawberries	0.02 / -	0.3	Medlar	0.02 / -
No of critical MRLs (IESTI 1)			---			**No of critical MRLs (IESTI 2)**			---		

Processed commodities

No of commodities for which ARfD/ADI is exceeded: ---				No of commodities for which ARfD/ADI is exceeded: ---		
		***)				***)
Highest % of ARfD/ADI	Processed commodities	pTMRL/ threshold MRL (mg/kg)		Highest % of ARfD/ADI	Processed commodities	pTMRL/ threshold MRL (mg/kg)
3.4	Apple juice	0.02 / -		0.4	Apple juice	0.02 / -
1.2	Pear juice	0.02 / -		0.1	Quince jelly	0.02 / -
0.1	Quinces jelly	0.02 / -				

*) 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.
**) pTMRL: provisional temporary MRL
***) pTMRL: provisional temporary MRL for unprocessed commodity

Conclusion:

For milbemectin 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.

APPENDIX C – EXISTING EU MAXIMUM RESIDUE LIMITS (MRLS)

(Pesticides - Web Version - EU MRLs (File created on 28/03/2011 12:16)

Code number	Groups and examples of individual products to which the MRLs apply (a)	Milbemectin (sum of MA4+8,9Z-MA4, expressed as milbemectin) (R)
100000	1. FRUIT FRESH OR FROZEN; NUTS	
110000	(i) Citrus fruit	0,05*
110010	Grapefruit (Shaddocks, pomelos, sweeties, tangelo, ugli and other hybrids)	0,05*
110020	Oranges (Bergamot, bitter orange, chinotto and other hybrids)	0,05*
110030	Lemons (Citron, lemon)	0,05*
110040	Limes	0,05*
110050	Mandarins (Clementine, tangerine and other hybrids)	0,05*
110990	Others	0,05*
120000	(ii) Tree nuts (shelled or unshelled)	0,1*
120010	Almonds	0,1*
120020	Brazil nuts	0,1*
120030	Cashew nuts	0,1*
120040	Chestnuts	0,1*
120050	Coconuts	0,1*
120060	Hazelnuts (Filbert)	0,1*
120070	Macadamia	0,1*
120080	Pecans	0,1*
120090	Pine nuts	0,1*
120100	Pistachios	0,1*
120110	Walnuts	0,1*
120990	Others	0,1*
130000	(iii) Pome fruit	0,05*
130010	Apples (Crab apple)	0,05*
130020	Pears (Oriental pear)	0,05*
130030	Quinces	0,05*
130040	Medlar	0,05*
130050	Loquat	0,05*
130990	Others	0,05*
140000	(iv) Stone fruit	0,05*
140010	Apricots	0,05*
140020	Cherries (sweet cherries, sour cherries)	0,05*
140030	Peaches (Nectarines and similar hybrids)	0,05*
140040	Plums (Damson, greengage, mirabelle)	0,05*
140990	Others	0,05*
150000	(v) Berries & small fruit	0,05*
151000	(a) Table and wine grapes	0,05*
151010	Table grapes	0,05*
151020	Wine grapes	0,05*
152000	(b) Strawberries	0,05*
153000	(c) Cane fruit	0,05*
153010	Blackberries	0,05*
153020	Dewberries (Loganberries, Boysenberries, and cloudberries)	0,05*
153030	Raspberries (Wineberries)	0,05*
153990	Others	0,05*
154000	(d) Other small fruit & berries	0,05*
154010	Blueberries (Bilberries cowberries (red bilberries))	0,05*
154020	Cranberries	0,05*
154030	Currants (red, black and white)	0,05*
154040	Gooseberries (Including hybrids with other ribes species)	0,05*
154050	Rose hips	0,05*
154060	Mulberries (arbutus berry)	0,05*
154070	Azarole (mediteranean medlar)	0,05*
154080	Elderberries (Black chokeberry (appleberry), mountain ash, azarole, buckthorn (sea sallowthorn), hawthorn, service berries, and other treeberries)	0,05*
154990	Others	0,05*
160000	(vi) Miscellaneous fruit	0,05*
161000	(a) Edible peel	0,05*
161010	Dates	0,05*
161020	Figs	0,05*
161030	Table olives	0,05*
161040	Kumquats (Marumi kumquats, nagami kumquats)	0,05*
161050	Carambola (Bilimbi)	0,05*
161060	Persimmon	0,05*
161070	Jambolan (java plum) (Java apple (water apple), pomerac, rose apple, Brazilean cherry (grumichama), Surinam cherry)	0,05*
161990	Others	0,05*
162000	(b) Inedible peel, small	0,05*
162010	Kiwi	0,05*
162020	Lychee (Litchi) (Pulasan, rambutan (hairy litchi))	0,05*
162030	Passion fruit	0,05*
162040	Prickly pear (cactus fruit)	0,05*
162050	Star apple	0,05*
162060	American persimmon (Virginia kaki) (Black sapote, white sapote, green sapote, canistel (yellow sapote), and mammey sapote)	0,05*
162990	Others	0,05*
163000	(c) Inedible peel, large	0,05*
163010	Avocados	0,05*
163020	Bananas (Dwarf banana, plantain, apple banana)	0,05*
163030	Mangoes	0,05*
163040	Papaya	0,05*
163050	Pomegranate	0,05*
163060	Cherimoya (Custard apple, sugar apple (sweetsop) , llama and other medium sized Annonaceae)	0,05*
163070	Guava	0,05*
163080	Pineapples	0,05*
163090	Bread fruit (Jackfruit)	0,05*
163100	Durian	0,05*
163110	Soursop (guanabana)	0,05*
163990	Others	0,05*
200000	2. VEGETABLES FRESH OR FROZEN	0,05*
210000	(i) Root and tuber vegetables	0,05*
211000	(a) Potatoes	0,05*
212000	(b) Tropical root and tuber vegetables	0,05*
212010	Cassava (Dasheen, eddoe (Japanese taro), tannia)	0,05*
212020	Sweet potatoes	0,05*
212030	Yams (Potato bean (yam bean), Mexican yam bean)	0,05*
212040	Arrowroot	0,05*
212990	Others	0,05*
213000	(c) Other root and tuber vegetables except sugar beet	0,05*
213010	Beetroot	0,05*
213020	Carrots	0,05*
213030	Celeriac	0,05*
213040	Horseradish	0,05*
213050	Jerusalem artichokes	0,05*
213060	Parsnips	0,05*
213070	Parsley root	0,05*
213080	Radishes (Black radish, Japanese radish, small radish and similar varieties)	0,05*
213090	Salsify (Scorzonera, Spanish salsify (Spanish oysterplant))	0,05*
213100	Swedes	0,05*
213110	Turnips	0,05*
213990	Others	0,05*
220000	(ii) Bulb vegetables	0,05*
220010	Garlic	0,05*
220020	Onions (Silverskin onions)	0,05*
220030	Shallots	0,05*
220040	Spring onions (Welsh onion and similar varieties)	0,05*
220990	Others	0,05*
230000	(iii) Fruiting vegetables	0,05*
231000	(a) Solanacea	0,05*
231010	Tomatoes (Cherry tomatoes,)	0,05*
231020	Peppers (Chilli peppers)	0,05*
231030	Aubergines (egg plants) (Pepino)	0,05*

Code number	Groups and examples of individual products to which the MRLs apply (a)	Milbemectin (sum of MA4+8,9Z-MA4, expressed as milbemectin) (R)
231040	Okra, lady's fingers	0,05*
231990	Others	0,05*
232000	(b) Cucurbits - edible peel	0,05*
232010	Cucumbers	0,05*
232020	Gherkins	0,05*
232030	Courgettes (Summer squash, marrow (patisson))	0,05*
232990	Others	0,05*
233000	(c) Cucurbits-inedible peel	0,05*
233010	Melons (Kiwano)	0,05*
233020	Pumpkins (Winter squash)	0,05*
233030	Watermelons	0,05*
233990	Others	0,05*
234000	(d) Sweet corn	0,05*
239000	(e) Other fruiting vegetables	0,05*
240000	(iv) Brassica vegetables	0,05*
241000	(a) Flowering brassica	0,05*
241010	Broccoli (Calabrese, Chinese broccoli, Broccoli raab)	0,05*
241020	Cauliflower	0,05*
241990	Others	0,05*
242000	(b) Head brassica	0,05*
242010	Brussels sprouts	0,05*
242020	Head cabbage (Pointed head cabbage, red cabbage, savoy cabbage, white cabbage)	0,05*
242990	Others	0,05*
243000	(c) Leafy brassica	0,05*
243010	Chinese cabbage (Indian (Chinese) mustard, pak choi, Chinese flat cabbage (tai goo choi), peking cabbage (pe-tsai), cow cabbage)	0,05*
243020	Kale (Borecole (curly kale), collards)	0,05*
243990	Others	0,05*
244000	(d) Kohlrabi	0,05*
250000	(v) Leaf vegetables & fresh herbs	0,05*
251000	(a) Lettuce and other salad plants including Brassicacea	0,05*
251010	Lamb´s lettuce (Italian comsalad)	0,05*
251020	Lettuce (Head lettuce, lollo rosso (cutting lettuce), iceberg lettuce, romaine (cos) lettuce)	0,05*
251030	Scarole (broad-leaf endive) (Wild chicory, red-leaved chicory, radicchio, curld leave endive, sugar loaf)	0,05*
251040	Cress	0,05*
251050	Land cress	0,05*
251060	Rocket, Rucola (Wild rocket)	0,05*
251070	Red mustard	0,05*
251080	Leaves and sprouts of Brassica spp (Mizuna)	0,05*
251990	Others	0,05*
252000	(b) Spinach & similar (leaves)	0,05*
252010	Spinach (New Zealand spinach, turnip greens (turnip tops))	0,05*
252020	Purslane (Winter purslane (miner's lettuce), garden purslane, common purslane, sorrel, glassworth)	0,05*
252030	Beet leaves (chard) (Leaves of beetroot)	0,05*
252990	Others	0,05*
253000	(c) Vine leaves (grape leaves)	0,05*
254000	(d) Water cress	0,05*
255000	(e) Witloof	0,05*
256000	(f) Herbs	0,05*
256010	Chervil	0,05*
256020	Chives	0,05*
256030	Celery leaves (fennel leaves , Coriander leaves, dill leaves, Caraway leaves, lovage, angelica, sweet cisely and other Apiacea)	0,05*
256040	Parsley	0,05*
256050	Sage (Winter savory, summer savory,)	0,05*
256060	Rosemary	0,05*
256070	Thyme (marjoram, oregano)	0,05*
256080	Basil (Balm leaves, mint, peppermint)	0,05*
256090	Bay leaves (laurel)	0,05*
256100	Tarragon (Hyssop)	0,05*
256990	Others	0,05*
260000	(vi) Legume vegetables (fresh)	0,05*
260010	Beans (with pods) (Green bean (french beans, snap beans), scarlet runner bean, slicing bean, yardlong beans)	0,05*
260020	Beans (without pods) (Broad beans, Flageolets, jack bean, lima bean, cowpea)	0,05*
260030	Peas (with pods) (Mangetout (sugar peas))	0,05*
260040	Peas (without pods) (Garden pea, green pea, chickpea)	0,05*
260050	Lentils	0,05*
260990	Others	0,05*
270000	(vii) Stem vegetables (fresh)	0,05*
270010	Asparagus	0,05*
270020	Cardoons	0,05*
270030	Celery	0,05*
270040	Fennel	0,05*
270050	Globe artichokes	0,05*
270060	Leek	0,05*
270070	Rhubarb	0,05*
270080	Bamboo shoots	0,05*
270090	Palm hearts	0,05*
270990	Others	0,05*
280000	(viii) Fungi	0,05*
280010	Cultivated (Common mushroom, Oyster mushroom, Shi-take)	0,05*
280020	Wild (Chanterelle, Truffle, Morel ,)	0,05*
280990	Others	0,05*
290000	(ix) Sea weeds	0,05*
300000	3. PULSES, DRY	0,05*
300010	Beans (Broad beans, navy beans, flageolets, jack beans, lima beans, field beans, cowpeas)	0,05*
300020	Lentils	0,05*
300030	Peas (Chickpeas, field peas, chickling vetch)	0,05*
300040	Lupins	0,05*
300990	Others	0,05*
400000	4. OILSEEDS AND OILFRUITS	
401000	(i) Oilseeds	0,1*
401010	Linseed	0,1*
401020	Peanuts	0,1*
401030	Poppy seed	0,1*
401040	Sesame seed	0,1*
401050	Sunflower seed	0,1*
401060	Rape seed (Bird rapeseed, turnip rape)	0,1*
401070	Soya bean	0,1*
401080	Mustard seed	0,1*
401090	Cotton seed	0,1*
401100	Pumpkin seeds	0,1*
401110	Safflower	0,1*
401120	Borage	0,1*
401130	Gold of pleasure	0,1*
401140	Hempseed	0,1*
401150	Castor bean	0,1*
401990	Others	0,1*
402000	(ii) Oilfruits	
402010	Olives for oil production	0,05*
402020	Palm nuts (palmoil kernels)	0,1*
402030	Palmfruit	0,1*
402040	Kapok	0,1*
402990	Others	0,1*
500000	5. CEREALS	0,05*
500010	Barley	0,05*
500020	Buckwheat	0,05*
500030	Maize	0,05*
500040	Millet (Foxtail millet, teff)	0,05*
500050	Oats	0,05*
500060	Rice	0,05*
500070	Rye	0,05*
500080	Sorghum	0,05*
500090	Wheat (Spelt Triticale)	0,05*
500990	Others	0,05*
600000	6. TEA, COFFEE, HERBAL INFUSIONS AND COCOA	0,1*
610000	(i) Tea (dried leaves and stalks, fermented or otherwise of Camellia sinensis)	0,1*
620000	(ii) Coffee beans	0,1*
630000	(iii) Herbal infusions (dried)	0,1*
631000	(a) Flowers	0,1*
631010	Camomille flowers	0,1*
631020	Hybiscus flowers	0,1*
631030	Rose petals	0,1*
631040	Jasmine flowers	0,1*
631050	Lime (linden)	0,1*
631990	Others	0,1*
632000	(b) Leaves	0,1*
632010	Strawberry leaves	0,1*

Code number	Groups and examples of individual products to which the MRLs apply (a)	Milbemectin (sum of MA4+8,9Z-MA4, expressed as milbemectin) (R)
632020	Rooibos leaves	0,1*
632030	Maté	0,1*
632990	Others	0,1*
633000	(c) Roots	0,1*
633010	Valerian root	0,1*
633020	Ginseng root	0,1*
633990	Others	0,1*
639000	(d) Other herbal infusions	0,1*
640000	(iv) Cocoa (fermented beans)	0,1*
650000	(v) Carob (st johns bread)	0,1*
700000	7. HOPS (dried) , including hop pellets and unconcentrated powder	0,1*
800000	8. SPICES	0,1*
810000	(i) Seeds	0,1*
810010	Anise	0,1*
810020	Black caraway	0,1*
810030	Celery seed (Lovage seed)	0,1*
810040	Coriander seed	0,1*
810050	Cumin seed	0,1*
810060	Dill seed	0,1*
810070	Fennel seed	0,1*
810080	Fenugreek	0,1*
810090	Nutmeg	0,1*
810990	Others	0,1*
820000	(ii) Fruits and berries	0,1*
820010	Allspice	0,1*
820020	Anise pepper (Japan pepper)	0,1*
820030	Caraway	0,1*
820040	Cardamom	0,1*
820050	Juniper berries	0,1*
820060	Pepper, black and white (Long pepper, pink pepper)	0,1*
820070	Vanilla pods	0,1*
820080	Tamarind	0,1*
820990	Others	0,1*
830000	(iii) Bark	0,1*
830010	Cinnamon (Cassia)	0,1*
830990	Others	0,1*
840000	(iv) Roots or rhizome	0,1*
840010	Liquorice	0,1*
840020	Ginger	0,1*
840030	Turmeric (Curcuma)	0,1*
840040	Horseradish	0,1*

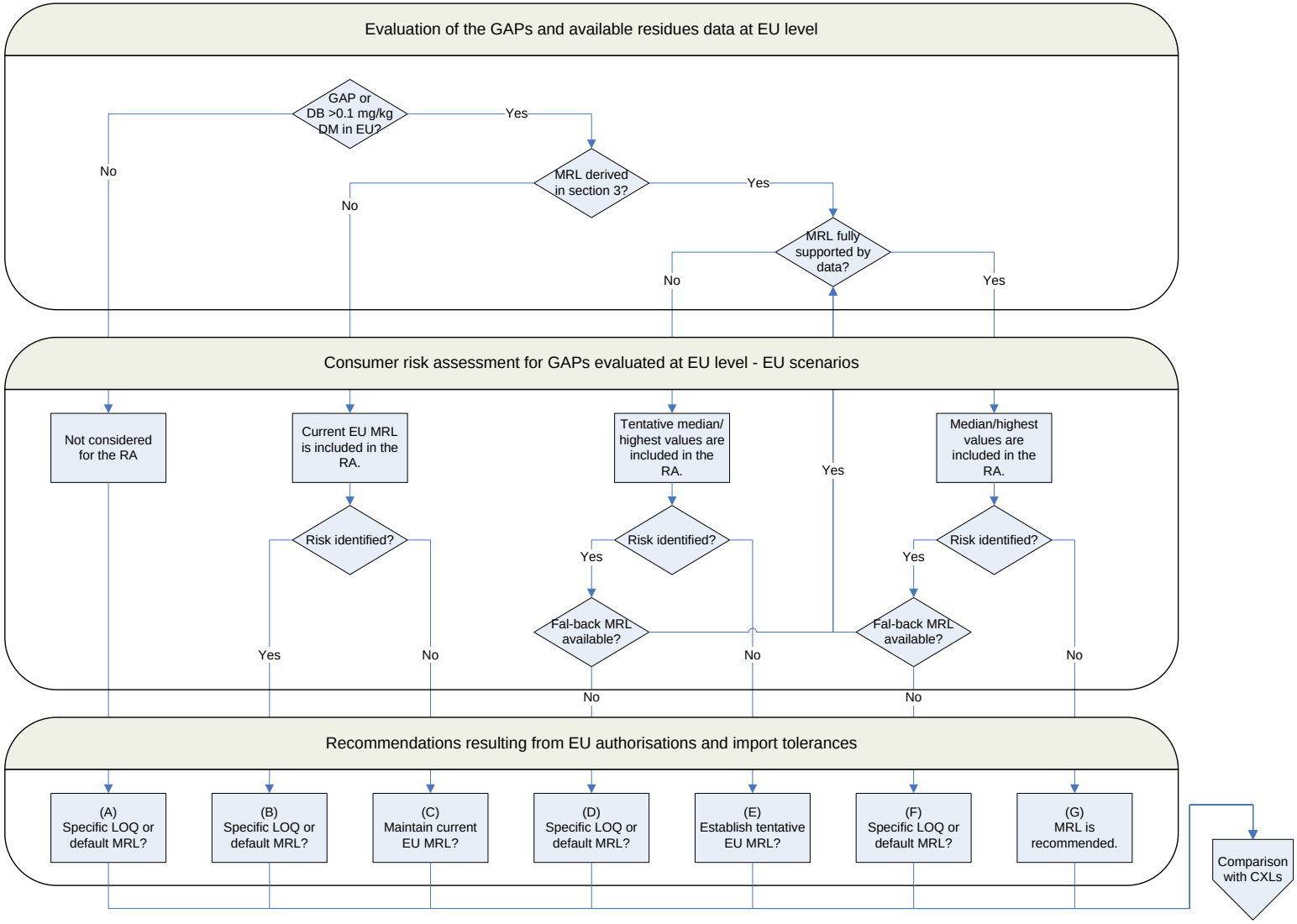
Code number	Groups and examples of individual products to which the MRLs apply (a)	Milbemectin (sum of MA4+8,9Z-MA4, expressed as milbemectin) (R)
840990	Others	0,1*
850000	(v) Buds	0,1*
850010	Cloves	0,1*
850020	Capers	0,1*
850990	Others	0,1*
860000	(vi) Flower stigma	0,1*
860010	Saffron	0,1*
860990	Others	0,1*
870000	(vii) Aril	0,1*
870010	Mace	0,1*
870990	Others	0,1*
900000	9. SUGAR PLANTS	0,05*
900010	Sugar beet (root)	0,05*
900020	Sugar cane	0,05*
900030	Chicory roots	0,05*
900990	Others	0,05*
1000000	10. PRODUCTS OF ANIMAL ORIGIN-TERRESTRIAL ANIMALS	
1010000	(i) Meat, preparations of meat, offals, blood, animal fats fresh chilled or frozen, salted, in brine, dried or smoked or processed as flours or meals other processed products such as sausages and food preparations based on these	
1011000	(a) Swine	
1011010	Meat	
1011020	Fat free of lean meat	
1011030	Liver	
1011040	Kidney	
1011050	Edible offal	
1011990	Others	
1012000	(b) Bovine	
1012010	Meat	
1012020	Fat	
1012030	Liver	
1012040	Kidney	
1012050	Edible offal	
1012990	Others	
1013000	(c) Sheep	
1013010	Meat	
1013020	Fat	
1013030	Liver	
1013040	Kidney	

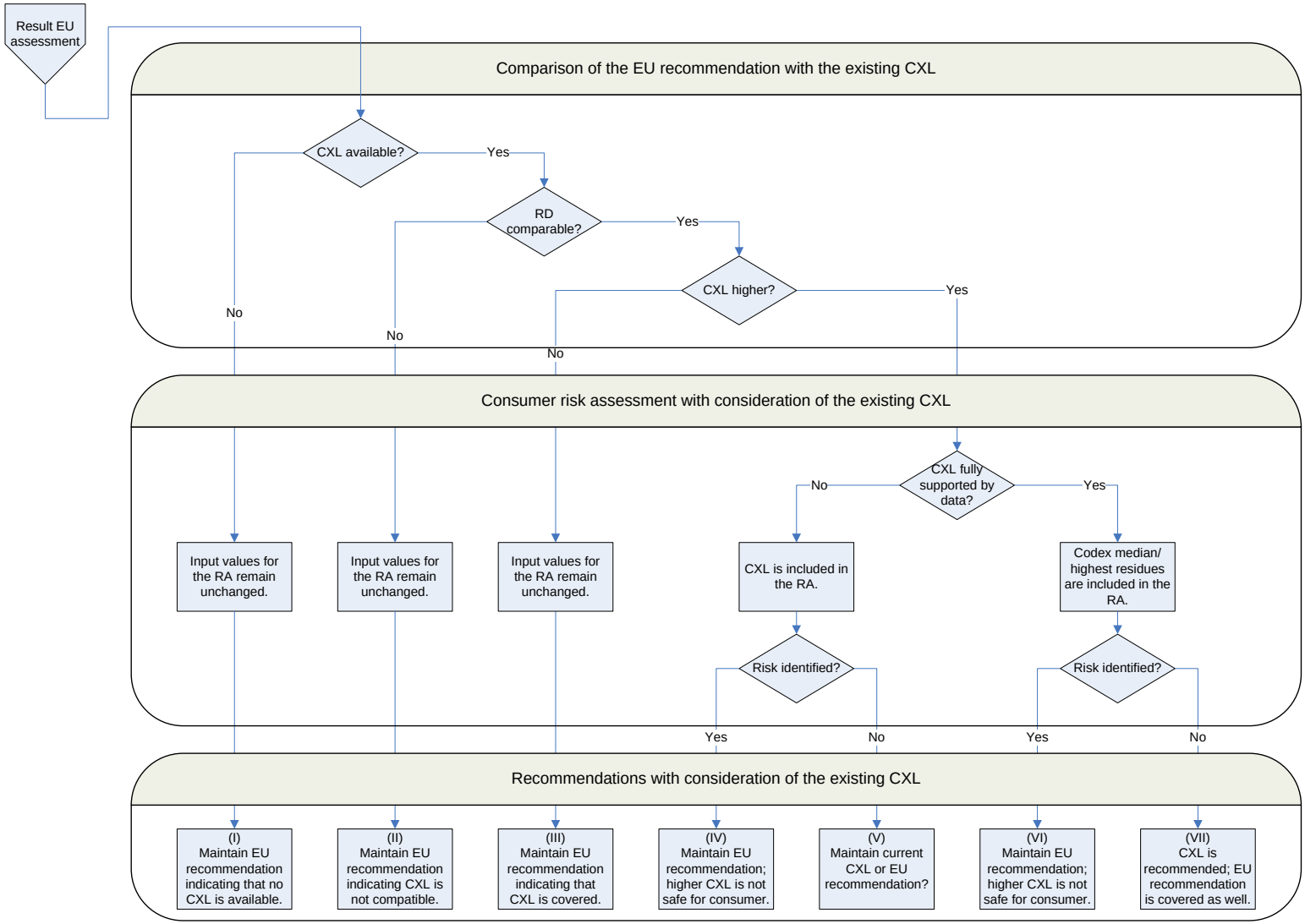
Code number	Groups and examples of individual products to which the MRLs apply (a)	Milbemectin (sum of MA4+8,9Z-MA4, expressed as milbemectin) (R)
1013050	Edible offal	
1013990	Others	
1014000	(d) Goat	
1014010	Meat	
1014020	Fat	
1014030	Liver	
1014040	Kidney	
1014050	Edible offal	
1014990	Others	
1015000	(e) Horses, asses, mules or hinnies	
1015010	Meat	
1015020	Fat	
1015030	Liver	
1015040	Kidney	
1015050	Edible offal	
1015990	Others	
1016000	(f) Poultry -chicken, geese, duck, turkey and Guinea fowl-, ostrich, pigeon	
1016010	Meat	
1016020	Fat	
1016030	Liver	
1016040	Kidney	
1016050	Edible offal	
1016990	Others	
1017000	(g) Other farm animals (Rabbit, Kangaroo)	
1017010	Meat	
1017020	Fat	
1017030	Liver	
1017040	Kidney	
1017050	Edible offal	
1017990	Others	
1020000	(ii) Milk and cream, not concentrated, nor containing added sugar or sweetening matter, butter and other fats derived from milk, cheese and curd	
1020010	Cattle	
1020020	Sheep	
1020030	Goat	
1020040	Horse	
1020990	Others	
1030000	(iii) Birds' eggs, fresh preserved or cooked Shelled eggs and egg	

Code number	Groups and examples of individual products to which the MRLs apply (a)	Milbemectin (sum of MA4+8,9Z-MA4, expressed as milbemectin) (R)
	yolks fresh, dried, cooked by steaming or boiling in water, moulded, frozen or otherwise preserved whether or not containing added sugar or sweetening matter	
1030010	Chicken	
1030020	Duck	
1030030	Goose	
1030040	Quail	
1030990	Others	
1040000	(iv) Honey (Royal jelly, pollen)	
1050000	(v) Amphibians and reptiles (Frog legs, crocodiles)	
1060000	(vi) Snails	
1070000	(vii) Other terrestrial animal products	

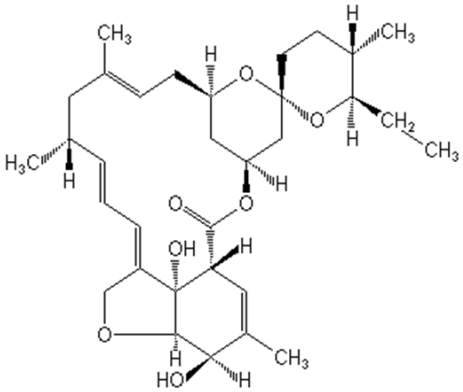
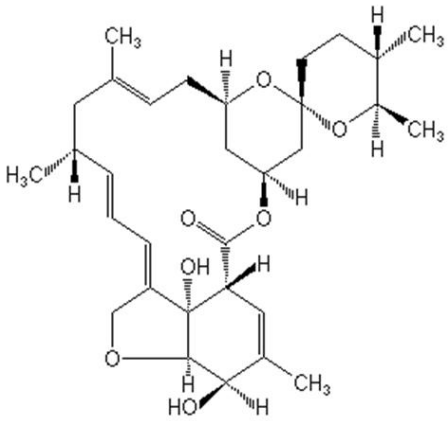
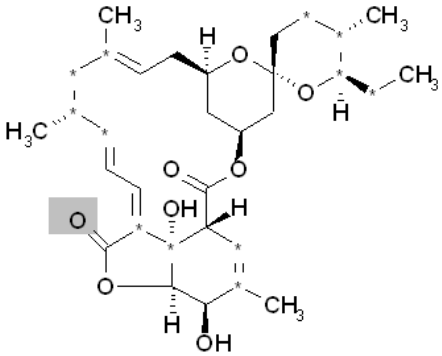
(*) Indicates lower limit of analytical determination

APPENDIX D – DECISION TREE FOR DERIVING MRL RECOMMENDATIONS




Result EU assessment
Comparison of the EU recommendation with the existing CXL
CXL available?
Yes
RD comparable?
Yes
CXL higher?
Yes
No
No
No
Consumer risk assessment with consideration of the existing CXL
CXL fully supported by data?
No
Yes
Input values for the RA remain unchanged.
Input values for the RA remain unchanged.
Input values for the RA remain unchanged.
CXL is included in the RA.
Codex median/ highest residues are included in the RA.
Risk identified?
Risk identified?
Yes
No
Yes
No
Recommendations with consideration of the existing CXL
(I) Maintain EU recommendation indicating that no CXL is available.
(II) Maintain EU recommendation indicating CXL is not compatible.
(III) Maintain EU recommendation indicating that CXL is covered.
(IV) Maintain EU recommendation; higher CXL is not safe for consumer.
(V) Maintain current CXL or EU recommendation?
(VI) Maintain EU recommendation; higher CXL is not safe for consumer.
(VII) CXL is recommended; EU recommendation is covered as well.

APPENDIX E – LIST OF METABOLITES AND RELATED STRUCTURAL FORMULA

Common name	IUPAC name	Structural formula
milbemycin A_4 (MA_4)	(10E,14E,16E,22Z)-(1R,4S,5'S,6R,6'R,8R,13R,20R,21R,24S)-6'-ethyl-21,24-dihydroxy-5',11,13,22-tetramethyl-3,7,19-trioxatetracyclo[15.6.1.$1^{4.8}0^{20,24}$]pentacosa-10,14,16,22-tetraene-6-spiro-2'-tetrahydropyran-2-one	
milbemycin A_3 (MA_3)	(10E,14E,16E,22Z)-(1R,4S,5'S,6R,6'R,8R,13R,20R,21R,24S)-21,24-dihydroxy-5',6',11,13,22-pentamethyl-3,7,19-trioxatetracyclo[15.6.1.$1^{4.8}$.$0^{20,24}$]pentacosa-10,14,16,22-tetraene-6-spiro-2'-tetrahydropyran-2-one	
8,9-Z milbemycin A_4	Isomer of milbemycin A_4	Isomer of milbemycin A_4
8,9-Z milbemycin A_3	Isomer of milbemycin A_3	Isomer of milbemycin A_3
27-keto-milbemycin A_4 (27-keto-MA_4)	-	

ABBREVIATIONS

a.s.	active substance
ADI	acceptable daily intake
ARfD	acute reference dose
BBCH	growth stages of mono- and dicotyledonous plants
bw	body weight
CF	conversion factor for enforcement residue definition to risk assessment residue definition
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
EC	emulsifiable concentrate
EFSA	European Food Safety Authority
eq	residue expressed as a.s. equivalent
EU	European Union
FAO	Food and Agriculture Organisation of the United Nations
GAP	good agricultural practice
ha	hectare
hL	hectolitre
HPLC	high performance liquid chromatography
HPLC-MS/MS	high performance liquid chromatography with tandem mass spectrometry
ISO	International Organization for Standardization
IUPAC	International Union of Pure and Applied Chemistry
JMPR	Joint FAO/WHO Meeting on Pesticide Residues

L	litre
LOQ	limit of quantification
MRL	maximum residue limit
MS	Member States
NEU	northern European Union
PF	processing factor
PHI	pre-harvest interval
PRIMo	(EFSA) Pesticide Residues Intake Model
PROFile	(EFSA) Pesticide Residue 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
RSD	relative standard deviation
SEU	Southern European Union
TRR	total radioactive residue