



EUROPEAN COMMISSION
HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL

Directorate D - Food Safety: Production and distribution chain
Unit D.3 - Chemicals, contaminants and pesticides

Milbemectin
SANCO/10386/2002 -rev. final¹
04 April 2005

**COMMISSION WORKING DOCUMENT - DOES NOT NECESSARILY REPRESENT
THE VIEWS OF THE COMMISSION SERVICES**

Review report for the active substance **milbemectin**

Finalised in the Standing Committee on the Food Chain and Animal Health at its meeting on 3 June 2005 in view of the inclusion of milbemectin in Annex I of Directive 91/414/EEC.

1. Procedure followed for the evaluation process

This review report has been established as a result of the evaluation of the new active substance milbemectin, made in the context of the work provided for in Articles 5 and 6 of Directive 91/414/EEC concerning the placing of plant protection products on the market, with a view to the possible inclusion of this substance in Annex I to the Directive.

In accordance with the provisions of Article 6(2) of Directive 91/414/EEC, the Dutch authorities received on 06 March 2000 an application from Sankyo Company, Limited (now Sankyo Agro Company, Limited), hereafter referred to as the applicant, for the inclusion of the active substance milbemectin in Annex I to the Directive. The Dutch authorities indicated to the Commission on 02 May 2000 the results of a first examination of the completeness of the dossier, with regard to the data and information requirements provided for in Annex II and, for at least one plant protection product containing the active substance concerned, in Annex III to the Directive. Subsequently, and in accordance with the requirements of Article 6(2), a dossier on milbemectin was distributed to the Member States and the Commission.

The Commission referred the dossier to the Standing Committee on the Food Chain and Animal Health in the meeting of the working group 'legislation' thereof on 31 May 2000, during which the Member States confirmed the receipt of the dossier.

In accordance with the provisions of Article 6(3), which requires the confirmation at Community level that the dossier is to be considered as satisfying, in principle, the data and information requirements provided for in Annex II and, for at least one plant protection product containing the active substance concerned, in Annex III to the Directive and in accordance with the

¹ Final revision, as amended on 18 November 2005.

procedure laid down in Article 20 of the Directive, the Commission confirmed in its Decision 2000/540/EC² of 06 September 2000 that these requirements were satisfied.

Within the framework of that decision and with a view to the further organisation of the works related to the detailed examination of the dossier provided for in Article 6(2) and (4) of Directive 91/414/EEC, it was agreed between the Member States and the Commission that The Netherlands would, as rapporteur Member State, carry out the detailed examination of the dossier and report the conclusions of its examination accompanied by any recommendations on the inclusion or non-inclusion and any conditions relating thereto, to the Commission as soon as possible and at the latest within a period of one year.

The Netherlands submitted to the Commission on 16 June 2001 the report of its detailed scientific examination, hereafter referred to as the draft assessment report, including, as required, a recommendation concerning the possible inclusion of milbemectin in Annex I to the Directive.

On receipt of the draft assessment report, the Commission forwarded it for consultation to all the Member States as well as to Sankyo Company Limited being the sole applicant on 26 June 2002.

The Commission organised further an intensive consultation of specialised scientific experts from a representative number of Member States, to review the draft assessment report and the comments received thereon (peer review), in particular on each of the following disciplines :

- identity and physical /chemical properties ;
- fate and behaviour in the environment ;
- ecotoxicology ;
- mammalian toxicology ;
- residues and analytical methods ;
- regulatory questions.

The meetings for this consultation were organised on behalf of the Commission by the Biologische Bundesanstalt für Land und Forstwirtschaft (BBA) in Braunschweig, Germany, from October 2002 to July 2003.

The report of the peer review (i.e. full report) was circulated, for further consultation, to Member States and the sole applicant on 14 October 2003.

The dossier, draft assessment report and the peer review report (i.e. full report) including in particular an outline resumé of the remaining technical questions, were referred to the Standing Committee on the Food Chain and Animal Health, and specialised working groups of this Committee, for final examination, with participation of experts from all Member States. This final examination took place from January 2004 to June 2005, and was finalised in the meeting of the Standing Committee on 2 June 2005.

The present review report contains the conclusions of this final examination; given the importance of the draft assessment report, the peer review report (i.e. full report) and the comments and clarifications submitted after the peer review as basic information for the final examination process, these documents are considered respectively as background documents A, B and C to this review report and are part of it.

² OJ No L 230, 12.09.2000, p.14.

The review did not reveal any open questions or concerns, which would have required a consultation of the Scientific Committee on Plants or the Panel on Plant Health, Plant Protection Products and their Residues of the European Food Safety Authority.

2. Purposes of this review report

This review report, including the background documents and appendices thereto, have been developed and finalised in support of the Directive 2005/58/EC³ concerning the inclusion of milbemectin in Annex I to Directive 91/414/EEC, and to assist the Member States in decisions on individual plant protection products containing milbemectin they have to take in accordance with the provisions of that Directive, and in particular the provisions of article 4(1) and the uniform principles laid down in Annex VI.

This review report provides also for the evaluation required under Section A.2.(b) of the above mentioned uniform principles, as well as under several specific sections of part B of these principles. In these sections it is provided that Member States, in evaluating applications and granting authorisations, shall take into account the information concerning the active substance in Annex II of the directive, submitted for the purpose of inclusion of the active substance in Annex I, as well as the result of the evaluation of those data.

In parallel with the provisions of Article 7(6) of Regulation 3600/92 for existing active substances, the Commission and the Member States will keep available or make available this review report for consultation by any interested parties or will make it available to them on their specific request. Moreover the Commission will send a copy of this review report (not including the background documents) to the applicant.

The information in this review report is, at least partly, based on information which is confidential and/or protected under the provisions of Directive 91/414/EEC. It is therefore recommended that this review report would not be accepted to support any registration outside the context of Directive 91/414/EEC, e.g. in third countries, for which the applicant has not demonstrated possession of regulatory access to the information on which this review report is based.

3. Overall conclusion in the context of Directive 91/414/EEC

The overall conclusion from the evaluation is that it may be expected that plant protection products containing milbemectin will fulfil the safety requirements laid down in Article 5(1)(a) and (b) of Directive 91/414/EEC. This conclusion is however subject to compliance with the particular requirements in sections 4, 5, 6 and 7 of this report, as well as to the implementation of the provisions of Article 4(1) and the uniform principles laid down in Annex VI of Directive 91/414/EEC, for each milbemectin containing plant protection product for which Member States will grant or review the authorisation.

Furthermore, these conclusions were reached within the framework of the uses which were proposed and supported by the sole data submitter and mentioned in the list of uses supported by available data (attached as Appendix IV to this Review Report).

³ OJ No L 246, 22.09.05, p. 17-19

Extension of the use pattern beyond those described above will require an evaluation at Member State level in order to establish whether the proposed extensions of use can satisfy the requirements of Article 4(1) and of the uniform principles laid down in Annex VI of Directive 91/414/EEC.

4. Specific conclusions which are highlighted in this evaluation

4.1 Residues of milbemectin in foodstuffs

The review has established that the residues arising from the proposed uses, consequent on application consistent with good plant protection practice, have no harmful effects on human or animal health. The Theoretical Maximum Daily Intake (TMDI) for a 60 kg adult is 0.078% of the Acceptable Daily Intake (ADI), based on the FAO/WHO European Diet (August 1994). This low intake value reflects the current limited use pattern for this active substance.

Estimates of acute dietary exposure of adults and children revealed that the Acute Reference Dose (ARfD) would not be exceeded (respectively 1.6% and 5.4% of the ARfD for adults and children).

4.2 Exposure of operators, workers and bystanders

The review has identified acceptable exposure scenarios for operators, workers and bystanders, which require, however, confirmation for each plant protection product in accordance with the relevant sections of the above mentioned uniform principles.

4.3 Ecotoxicology

The review has also concluded that under the proposed and supported conditions of use there are no unacceptable effects on the environment, as provided for in Article 4 (1) (b) (iv) and (v) of Directive 91/414/EEC, provided that certain conditions are taken into account as detailed in section 7 of this report.

5. Identity and Physical/chemical properties

The main identity and the physical/chemical properties of milbemectin are given in Appendix I.

The active substance shall have a minimum purity of 950 g/kg technical product, consisting of a mixture of milbemycin A₃ (M.A₃) and milbemycin A₄ (M.A₄) (ratio 30:70).

The review has established that for the active substance notified by the applicant, none of the manufacturing impurities considered are, on the basis of information currently available, of toxicological or environmental concern.

6. Endpoints and related information

In order to facilitate Member States, in granting or reviewing authorisations, to apply adequately the provisions of Article 4(1) of Directive 91/414/EEC and the uniform principles laid down in

Annex VI of that Directive, the most important endpoints as identified during the evaluation process are listed in Appendix II.

7. Particular conditions to be taken into account on short term basis by Member States in relation to the granting of authorisations of plant protection products containing milbemectin

On the basis of the proposed and supported uses, the following particular issues have been identified as requiring particular and short term (within 12 months at the latest) attention from the Member States, in the framework of any authorisations to be granted, varied or withdrawn, as appropriate:

In this overall assessment Member States should pay particular attention to the protection of aquatic organisms.

Risk mitigation measures should be applied where appropriate.

8. List of studies to be generated

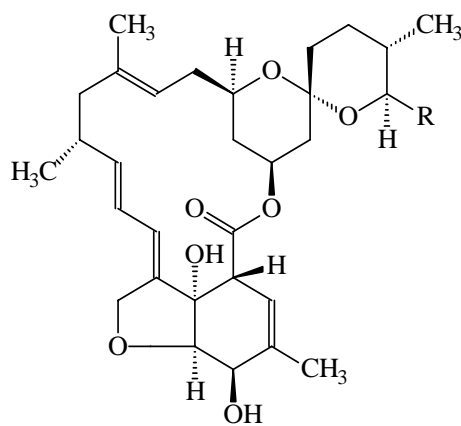
No further studies were identified which were considered at this stage, and under the current inclusion conditions necessary in relation to the inclusion of milbemectin in Annex I.

9. Updating of this review report

The technical information in this report may require periodic updating to take account of technical and scientific developments as well as of the results of the examination of any information referred to the Commission in the framework of Articles 7, 10 or 11 of Directive 91/414/EEC. Such adaptations will be examined and finalised in the Standing Committee on the Food Chain and Animal Health, in connection with any amendment of the inclusion conditions for milbemectin in Annex I of the Directive.

APPENDIX I**Identity, physical and chemical properties****MILBEMECTIN**

Common name (ISO)	Milbemectin is a mixture of milbemycin A ₃ (M.A ₃) and milbemycin A ₄ (M.A ₄) (ratio 30 : 70)	
Development Code (for new actives only)	B-41 and E-187	
Chemical name (IUPAC)	Milbemycin A ₃	Milbemycin A ₄
	(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	(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
Chemical name (CA)	(6R,25R)-5-O-demethyl-28-deoxy-6,28-epoxy-25-methylmilbemycin B	(6R,25R)-5-O-demethyl-28-deoxy-6,28-epoxy-25-ethylmilbemycin B
CIPAC No	660	
CAS No	51596-10-2	51596-11-3
EEC No	none	none
FAO SPECIFICATION	not established	
Minimum purity	Minimum 950 g/kg, consisting of a mixture of M.A ₃ and M.A ₄	
Molecular formula	C ₃₁ H ₄₄ O ₇	C ₃₂ H ₄₆ O ₇
Molecular mass	528.7	542.7

Structural formulaMilbemycin A₃: R=CH₃Milbemycin A₄: R=CH₂CH₃

	Milbemycin A ₃	Milbemycin A ₄
Melting point	236 - 243 °C (99.97% pure)	191 - 196 °C (98.45% pure)
Boiling point	Not required	Not required
Appearance	Milbemectin 99.01 % (28.62 % MA ₃ / 70.39 % MA ₄): crystalline, white, odourless and Milbemectin 98.01 % (26.22 % MA ₃ / 71.79 % MA ₄) powdered solid, white, odourless. MA ₄ (98.45% pure) and MA ₃ (99.97% pure) crystalline, white, odourless	
Relative density	Milbemectin 99.01 % (28.62 % MA ₃ / 70.39 % MA ₄) 1.119 and Milbemectin 98.01 % (26.22 % MA ₃ / 71.79 % MA ₄) 1.144 MA ₄ (>99.9% pure) 1.1265 and MA ₃ (>99.9% pure) 1.1270	
Vapour pressure	< 1.3 x 10 ⁻⁵ (25°C)	
	9.7 x 10 ⁻¹² (20°C)	4.3 x 10 ⁻¹⁰ (20°C)
Henry's law constant	< 9.93 x 10 ⁻⁴	
	2.56 x 10 ⁻³	1.55 x 10 ⁻³
Solubility in water	2.68 mg/l at 20 °C pH influence unlikely, due to structure	4.55 mg/l at 20 °C pH influence unlikely, due to structure
Solubility in organic solvents	for the MA ₄ /MA ₃ sample	(g/kg) at 25 °C
	Acetone	243
	n-Octanol	42.2
	n-Heptane	5.06
	o-Xylene	284
	1,2-Dichloroethane	> 250
	Methanol	251
	Ethyl acetate	250
Partition co-efficient (log P_{ow})	6.54 at 25 °C, neutral conditions	7.0 at 25 °C, neutral conditions
	Effect of pH (4 to 10) on the n-octanol/water partition is not required since milbemectin MA ₃ and MA ₄ is neither acidic nor basic.	
Hydrolytic stability (DT₅₀)	pH	Hydrolysis Determined for M.A ₄ , but due to similarity of the molecule, it is unlikely that rate of degradation is much different.
	5	t _{1/2} = 11.6days
	7	t _{1/2} = 259.9 days
	9	t _{1/2} = 226.3 days

Dissociation constant	Not applicable because the molecular structures of milbemectin are neutral and have no dissociation constants.	
Quantum yield of direct photo-transformation in water at $\lambda > 290$ nm	$\Phi = 0.044$ Determined for M.A ₄ , but due to similarity of the molecule, it is unlikely that rate of degradation is much different.	
Flammability	Non-flammable	
Explosive properties	Not explosive	
UV/VIS absorption (max.)	At acidic, neutral and alkaline solutions: λ max. at 244 nm shoulders at 238 and 252nm	At acidic, neutral and alkaline solutions: λ max. at 244 nm shoulders at 238 and 252nm
Photostability in water (DT₅₀)	pH	Photolysis Determined for M.A ₄ , but due to similarity of the molecule, it is unlikely that rate of degradation is much different.
	5	t _{1/2} = 0.9 days
	7	t _{1/2} = 2.4 days
	9	t _{1/2} = 3.9 days

APPENDIX II

END POINTS AND RELATED INFORMATION

MILBEMECTIN

1 Toxicology and metabolism

Absorption, distribution, excretion and metabolism in mammals

Rate and extent of absorption:	At least 47% at single low dose (2.5 mg/kg bw), based on biliary and urinary excretion
Distribution:	Widely distributed; highest residues in adrenals, kidneys, pancreas, lymph nodes, and reproductive fat
Potential for accumulation:	No evidence for accumulation
Rate and extent of excretion:	Urinary: 5-9% in 24 h; faecal: 85-100% in 24 h
Toxicologically significant compounds:	Parent compound and metabolites
Metabolism in animals:	Extensively metabolised (no parent compound in faeces or bile at low dose) mainly by hydroxylation, also evidence for minor glucuronidation pathway

Acute toxicity

Rat LD ₅₀ oral:	456 mg/kg bw; R22
Rat LD ₅₀ dermal:	> 5000 mg/kg bw
Rat LC ₅₀ inhalation:	LC50 < 3 mg/l, (4h, whole body); R20
Skin irritation:	Not irritating
Eye irritation:	Not irritating
Skin sensitization (test method used and result):	Not sensitising (M&K)

Short term toxicity

Target / critical effect:	Liver (dog, hypertrophy), adrenals (rabbit), red blood cells (rat, increased hematopoiesis), clinical signs (dog, vomiting, neurotoxic findings)
Lowest relevant oral NOAEL / NOEL:	90-d and 12-mo dog: 3 mg/kg bw/d
Lowest relevant dermal NOAEL / NOEL:	28-d rabbit: 500 mg/kg bw/d
Lowest relevant inhalation NOAEL / NOEL:	No data – not required for the risk assessment of the formulation Milbeknock 1% EC, containing 1 % milbemectin

Genotoxicity

No genotoxic potential

Long term toxicity and carcinogenicity

Target / critical effect:

Kidney, adrenals, liver and uterus (rat)

Lowest relevant NOAEL:

104-wk rat: 15 ppm (0.7 mg/kg bw/d)

Carcinogenicity:

Increased incidence of neoplastic changes in uterus of rats.

Reproductive toxicity

Target / critical effect - Reproduction:

Decreased litter size, survival index and body weight of pups at parental toxic dose

Lowest relevant reproductive NOAEL / NOEL:

200 ppm (12.4 mg/kg bw/d)

Target / critical effect - Developmental toxicity:

No effects in rats at maternal toxic dose level; in rabbits abortion and reduced fetal weight at maternal toxic dose levels

Lowest relevant developmental NOAEL / NOEL:

Rabbit: 50 mg/kg bw/d

Delayed neurotoxicity

acute neurotoxicity NOAEL

< 20 mg/kg bw; (NOAEL obtained by extrapolation: 3 mg/kg bw)

semi-chronic neurotoxicity NOAEL

13-wk rat: 750 ppm (59 mg/kg bw/d)

Other toxicological studiesEffects on central nervous system and at neuromuscular level in several *in vivo* and *in vitro* experiments. The photoisomers 8,9Z-MA3 and 8,9Z-MA4 showed no genotoxic potential.**Medical data**

No evidence of toxicological concern from annual medical examinations of manufacturing plant personnel, no cases of poisoning reported.

Summary

	Value	Study	Safety factor
ADI:	0.03 mg/kg bw/d	12-month oral dog	100
AOEL systemic:	0.014 mg/kg bw/d	90-d oral dog	100, 47% oral absorption
AOEL inhalation:	Not applicable		
AOEL dermal:	Not applicable		
ARfD (acute reference dose):	0.03 mg/kg bw/d	90-d and 12-month dog (supported by acute oral neurotoxicity rat, NOAEL derived by extrapolation)	100

Dermal absorption

Default value: 10% (based on phys.-chem. properties)
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2 Fate and behaviour in the environment

2.1 Fate and behaviour in soil

Route of degradation

Aerobic:

Mineralization after 100 days:

milbemyacin A₃
not available
milbemyacin A₄
14 – 35% of AR (after 120 days)

Non-extractable residues after 100 days:

milbemyacin A₃
not available
milbemyacin A₄
13 – 40% of AR (after 91 and/or 120 days)

Major metabolites above 10 % of applied active substance: name and/or code % of applied rate (range and maximum)

milbemyacin A₃
not available
milbemyacin A₄
27-hydroxy-milbemyacin A₄: 14% of AR after 27 days (ageing phase of column leaching test)
27-keto-milbemyacin A₄: 12% of AR, after 24 and 46 days

Supplemental studies

Anaerobic:

milbemyacin A₃
not available
milbemyacin A₄
non-extractable residue: maximum 22% after 363 days
mineralisation: 1.9% of AR after 363 days
no degradation products occurring at levels >10% of AR

Soil photolysis:

milbemyacin A₃
not available
milbemyacin A₄
non-extractable residue: maximum 29% after 21 days (end of study)
mineralisation: 12% of AR after 21 days
no degradation products occurring at levels >10% of AR

Remarks:

None

Rate of degradation

Laboratory studies

DT₅₀lab (20 °C, aerobic):

DT_{50, lab} (20°C, aerobic):

milbemycin A₃

not available

milbemycin A₄

21 days ($r^2=0.97$), 47 days ($r^2=0.97$), 82 days ($r^2=0.97$) and 22 days ($r^2=0.97$)

average DT₅₀ value: 43 days

27-hydroxy-milbemycin A₄

33 days ($r^2 = 0.91$), 23 days ($r^2 = 0.98$) and 32 days ($r^2 = 0.93$)

average DT₅₀ value: 29 days

27-keto-milbemycin A₄

52 days ($r^2 = 0.97$), 110 days ($r^2 = 0.94$) and 62 days ($r^2 = 0.98$)

average DT₅₀ value: 75 days

DT₉₀lab (20 °C, aerobic):

DT_{90, lab} (20°C, aerobic):

milbemycin A₃

not available

milbemycin A₄

143 days (extrapolated from DT₅₀ value

assuming first order exponential decay: $3.3 \cdot DT_{50}$)

DT₅₀lab (10 °C, aerobic):

DT_{50, lab} (10°C, aerobic):

milbemycin A₃

not available

milbemycin A₄

63 days ($r^2 = 0.97$)

Q₁₀ value: 3 (63/21)

27-hydroxy-milbemycin A₄

18 days ($r^2 = 0.97$)

DT₅₀lab (20 °C, anaerobic):

DT_{50, lab} (20°C, anaerobic):

milbemycin A₃

not available

milbemycin A₄

556 days ($r^2 = 0.85$)

Field studies (country or region)DT_{50f} from soil dissipation studies:DT_{50, field}:**milbemycin A₃**

New York, 8.1 days (n=1)

Florida 8.8 days (n=1)

milbemycin A₄

New York, 10.0 days (n=1)

Florida, 12.9 days (n=1)

DT_{90f} from soil dissipation studies:

not available, not required

Soil accumulation studies:

not required

Soil residue studies:

not required

Remarks:

e.g. effect of soil pH on degradation rate

none

Adsorption/desorption

K_f / K_{oc} :

K_d :

pH dependence:

milbemycin A₃

not available

based on the high hydrophobicity of both milbemycin A₃ and A₄, it is assumed that milbemycin A₃ has adsorption characteristics equal to milbemycin A₄

milbemycin A₄

K_F values: 12, 31, 57, and 153 dm³/kg

Corresponding K_{om} values: 1220, 910, 1970, and 2590 dm³/kg (average 1670 dm³/kg)

Corresponding K_{oc} values (assuming 59% organic carbon in organic matter): 2070, 1550, 3350, and 4400 dm³/kg (average 2840 dm³/kg; average 1/n 0.98)

no pH dependence

27-Hydroxy-MA4

K_F values: 94, 20 and 51 dm³/kg

Corresponding K_{oc} values: 2043, 2462 and 1828 dm³/kg (average 2111 dm³/kg; average 1/n 0.82)

27-Keto-MA4

K_F values: 246, 59 and 208 dm³/kg

Corresponding K_{oc} values: 5350, 7360 and 7444 dm³/kg (average 6718 dm³/kg; average 1/n 0.99)

Mobility

Laboratory studies:

Column leaching:

Aged residue leaching:

not required

milbemycin A₃

not available

milbemycin A₄

after 14 – 27 days ageing, reducing milbemycin A₄ to 37 – 55% of AR, and with 2.4 – 14% of AR present as 27-hydroxy-milbemycin A₄, and 1.9 – 12% of AR present as 27-keto-milbemycin A₄

81 – 97% of AR after ageing was recovered from the aged soil layer, except in the sand columns, where 52 and 70% of AR after ageing were recovered from the treated soil layer

1.0 – 3.3% of AR was recovered from the leachate, and the leachate never contained milbemycin A₄, 27-hydroxy-milbemycin A₄, or 27-keto-milbemycin A₄

the degradation products 27-hydroxy- and 27-keto-milbemycin A₄ were detected in layers below the treated soil layer in sand, where in one column 4.0% of radioactivity applied after ageing was extracted from the second layer, and 3.0% from the third layer as 27-hydroxy-milbemycin A₄, and in the other sand column, where 5.9% and 5.2% of AR after ageing was extracted from the second layer as 27-hydroxy- and 27-keto-milbemycin A₄ respectively

in the other soil types (sandy loam, silt loam and clay loam) these products were never detected below the treated soil layer

Field studies:

Lysimeter/Field leaching studies:

not required

Remarks:

none

2.2 Fate and behaviour in water

Abiotic degradation

Hydrolytic degradation:

<p>milbemycin A₃ not available</p> <p>milbemycin A₄ pH 5 (25°C): DT₅₀ 13 d 27-hydroxy-milbemycin A₄ highest level 8.2% of AR after 22 d 27-keto-milbemycin A₄ highest level 23% of AR after 21 d pH 7 (25°C): 8.5% hydrolysed after 31 d pH 9 (25°C): 9.7% hydrolysed after 31 d</p>
27-keto-milbemycin A ₄

Major metabolites:

Photolytic degradation:

<p>milbemycin A₃ not available</p> <p>milbemycin A₄ artificial sunlight, >290 nm, 25°C: pH 5: DT₅₀ 0.93 d, 6,11-dihydroxy-8-carboxy-milbemycin A₄: highest level 9.8% of AR after 2 d pH 7: DT₅₀ 2.6 d, 8,9Z-milbemycin A₄: highest level 13% of AR after 1.5 d pH 9: DT₅₀ 4.1 d, 8,9Z-milbemycin A₄: highest level 11% of AR after 2 d artificial light, 304 nm, 22 – 25°C: pH 6.9: DT₅₀ 7.8 h, quantum yield 0.044</p>
6,11-dihydroxy-8-carboxy-milbemycin A ₄ 8,9Z-milbemycin A ₄

Major metabolites:

Biological degradation

Readily biodegradable:

not readily biodegradable

Water/sediment study:

DT₅₀ water:

milbemycin A₃
not available

milbemycin A₄
1.8 d, 3.9 d
average DT₅₀ value: 2.9 d

DT₉₀ water:

milbemycin A₃
not available

milbemycin A₄
9.6 d (extrapolated from DT₅₀ value assuming first order exponential decay: 3.3·DT₅₀)

DT₅₀ whole system:

<p>milbemycin A₃ not available</p> <p>milbemycin A₄ 89 d, 82 d average DT₅₀ value: 86 d</p>
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DT₉₀ whole system:

<p>milbemycin A₃ not available</p> <p>milbemycin A₄ 286 d (extrapolated from DT₅₀ value assuming first order exponential decay: 3.3·DT₅₀)</p>

Distribution in water / sediment systems
(active substance)

<p>milbemycin A₃ not available</p> <p>milbemycin A₄ ¹⁴C-milbemycin A₄ dissipation from water was dominated by adsorption the sediment sediment extractable residue consisted mainly of ¹⁴C-milbemycin A₄, reaching average highest levels of 69% of AR after 7 days and 73% of AR after 30 days.</p>
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Distribution in water / sediment systems
(metabolites)

No degradation products detected in water or sediment at levels >10% of AR
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Accumulation in water and/or sediment:

not required

Degradation in the saturated zone

not required

Remarks:

none

2.3 Fate and behaviour in air

Volatility

Vapour pressure:

Henry's law constant:

Milbemycin A ₃	Milbemycin A ₄
$< 1.3 \times 10^{-5}$ (25°C)	
9.7×10^{-12} (20°C)	4.3×10^{-10} (20°C)
$< 9.93 \times 10^{-4}$	
2.56×10^{-3}	1.55×10^{-3}

Photolytic degradation

Direct photolysis in air:

Photochemical oxidative degradation in air

DT₅₀:

Volatilisation:

Remarks:

not available
Milbemycin A ₃ and A ₄ both have a vapour pressure of $< 1.3 \cdot 10^{-5}$ Pa, and Henry's law constants of $2.56 \cdot 10^{-3}$ and $1.55 \cdot 10^{-3}$ Pa·m ³ ·mol ⁻¹ respectively. Based on the information submitted it is considered that significant volatilisation of milbemycin A ₃ or A ₄ is unlikely to occur. Hydroxyl reaction and ozone reaction half-life were estimated to be 16.4 and 13.7 minutes respectively, by computer modelling. Should milbemycin A ₃ or A ₄ volatilise, then the compounds will degrade quickly.
from plant surfaces: not available
from soil: not available
none

3 Ecotoxicology

Terrestrial Vertebrates

Acute toxicity to mammals:	LD ₅₀ 456 mg/kg bw (rat) (milbemectin technical)
Acute toxicity to birds:	LD ₅₀ 347 mg/kg bw (mallard duck) (milbemectin technical)
Dietary toxicity to birds:	LC ₅₀ 1922 mg/kg feed (mallard duck) (milbemectin technical)
Reproductive toxicity to birds:	NOEC 150 mg/kg feed (milbemectin technical)
Short term oral toxicity to mammals:	Not required
Reproductive toxicity to mammals:	NOEC 200 mg/kg feed (milbemectin technical)

Aquatic Organisms

	Group	Test substance	Time-scale	Endpoint	Toxicity (mg as/L)
Acute toxicity fish:	<i>Lepomis macrochirus</i>	milbemectin technical	96 h	mortality, LC ₅₀ (flow-through)	0.028
	<i>Oncorhynchus mykiss</i>	milbemectin technical	96 h	mortality, LC ₅₀ (flow-through)	0.0044
	<i>Pimephales promelas</i>	milbemectin technical	96 h	mortality, LC ₅₀ (flow-through)	0.035
	<i>Cyprinus carpio</i>	milbemectin technical	96 h	mortality, LC ₅₀ (flow-through)	0.035
	<i>Cyprinodon variegatus</i>	milbemectin technical	96 h	mortality, LC ₅₀ (flow-through)	0.025
	<i>Oncorhynchus mykiss</i>	Milbeknock 1% EC	96 h	mortality, LC ₅₀ (flow-through)	0.0048
	<i>Oncorhynchus mykiss</i>	Milbeknock 1% EC	96 h	mortality, LC ₅₀ (static)	0.0057
	<i>Oncorhynchus mykiss</i>	Milbeknock 1% EC	96 h	mortality, LC ₅₀ (static + 0.4% OC sediment)	0.0102
Long term toxicity fish:	<i>Oncorhynchus mykiss</i>	milbemectin technical	88 d	ELS, NOEC	0.00065
Bioaccumulation fish:	milbemycin A3 76 L/kg ww, whole organism				
	milbemycin A4 114 L/kg ww, whole organism				

Acute toxicity
invertebrate:

<i>Daphnia magna</i>	milbemectin technical	48 h	immobility, EC ₅₀ (flow-through)	0.011	
<i>Daphnia magna</i>	Milbeknock 1% EC	48 h	immobility, EC ₅₀ (flow-through)	0.0044	
<i>Daphnia magna</i>	Milbeknock 1% EC	48 h	immobility, EC ₅₀ (static)	0.0053	
<i>Daphnia magna</i>	Milbeknock 1% EC	48 h	immobility, EC ₅₀ (static + 0.4% OC sediment)	0.0034	
Cladocera, Daphniidae	Milbeknock 1% EC	48 h	EC50 (static)	0.0627	
Copepoda, Cyclopoidae	Milbeknock 1% EC	48 h	EC50 (static)	0.0859	
Gastropoda (Planorbidae)	Milbeknock 1% EC	48 h	EC50 (static)	0.187	
Chironomidae	Milbeknock 1% EC	48 h	EC50 (static)	0.0301	
Tubificidae	Milbeknock 1% EC	48 h	EC50 (static)	1.142	
Chaoboridae	Milbeknock 1% EC	48 h	EC₅₀ (static)	0.0493	
Ephemeroptera, Baetidae	Milbeknock 1% EC	48 h	EC₅₀ (static)	0.461	
Chronic toxicity invertebrate:	<i>Daphnia magna</i>	milbemectin technical	21 d	reproduction, growth F1, NOEC	0.00012
Acute toxicity algae:	<i>Selenastrum capricornutum</i>	Milbeknock 1% EC	120 h	biomass, E _b C ₅₀ NOEC	0.22 0.038
	<i>Selenastrum capricornutum</i>	milbemectin technical	120 h	NOEC	2
	<i>Selenastrum capricornutum</i>	milbemectin technical	120 h	E _b C ₅₀ , EC ₅₀	>2
	Chronic toxicity sediment dwelling organism:	<i>Chironomus riparius</i>	Milbemectin technical	28 d	NOEC (static)

Honeybees

Acute oral toxicity:

LD₅₀ 0.40 µg/bee (technical material)

Acute contact toxicity:

LD₅₀ 0.026 µg/bee (technical material)

Hazard quotients for honey bees (Annex IIIA, point 10.4)				
Application/ rate (kg as/ha)	Crop	Route	Hazard quotient	Annex VI Trigger
Laboratory tests				
Field / 0.0188 (Germany)	apples	oral	In-field: 5 Off-field: 8*	50
Field / 0.0188 (Germany)	apples	contact	In-field: 72 Off-field: 112*	50
Field / 0.0174 (Italy, Spain, France)	apples	oral	In-field: 4 Off-field: 6.5*	50
Field / 0.0174 (Italy, Spain, France)	apples	contact	In-field: 67 Off-field: 104*	50
Field or semi-field tests				
Cage study with Milbeknock 1% EC				
- endpoints: mortality, foraging, brood				
- dosages: 27.9 as/ha (exposure to dried residues), 2.96 g as/ha (direct spray) and 7.5 g as/ha (direct spray)				
- effects: no effects at the three tested dosages				
* based on 15.73% spray drift (at 3m distance)				

Other arthropod species

<i>Test species</i>	Stage	Test Substance	Dose (g as/ha)	Endpoint	Effect (%)
<i>T. pyri</i>	protonymphs	Milbeknock 1% EC	25 and 42	mortality	100
<i>T. pyri</i>	protonymphs	Milbeknock 1% EC (leaves)	2.4 and 4.8	mortality	96 and 100
<i>T. pyri</i>	protonymphs	Milbeknock 1% EC (leaves)	1.2	mortality fecundity overall	29 77 84
<i>T. pyri</i>	protonymphs	Milbeknock 1% EC (leaves)	42	mortality	100
<i>T. pyri</i>	protonymphs	Milbeknock 1% EC (leaves)	42	mortality	65
<i>T. pyri</i>	protonymphs	Milbeknock 1% EC (leaves)	42	mortality	49
<i>T. pyri</i>	protonymphs	Milbeknock 1% EC (leaves)	34.8	mortality fecundity	81.5 nd

<i>T. pyri</i>	protonymphs	Milbeknock 1% EC (leaves)	5.394	mortality fecundity	12.9 1.6
<i>T. pyri</i>	protonymphs	Milbeknock 1% EC (leaves)	0.522	mortality fecundity	0 45.3
<i>T. pyri</i>	protonymphs	Milbeknock 1% EC (leaves)	3 x 30	mortality fecundity	71.4 nd
<i>T. pyri</i>	protonymphs	Milbeknock 1% EC (leaves; 7-days aged residues)	34.8	mortality fecundity	8.8 -56.9
<i>T. pyri</i>	protonymphs	Milbeknock 1% EC (leaves; 7-days aged residues)	5.394	mortality fecundity	2.9 -19.0

<i>T. pyri</i>	protonymphs	Milbeknock 1% EC (leaves; 7-days aged residues)	0.522	mortality fecundity	2.0 -50.0
<i>T. pyri</i>	protonymphs	Milbeknock 1% EC (leaves; 7-days aged residues)	3 x 30	mortality fecundity	7.4 -91.4
<i>C. carnea</i>	larvae	Milbeknock 1% EC (leaves)	9.3	mortality	8
<i>C. carnea</i>	larvae	Milbeknock 1% EC (leaves)	27.9	mortality	13
<i>C. carnea</i>	larvae	Milbeknock 1% EC (leaves)	27.9	mortality fecundity overall	21 no reduction 21
<i>O. laevigatus</i>	nymphs	Milbeknock 1% EC	25 and 42	mortality	100
<i>O. laevigatus</i>	nymphs	Milbeknock 1% EC (leaves)	9.3 and 27.9	mortality	22 and 41
<i>O. laevigatus</i>	nymphs	Milbeknock 1% EC (leaves)	9.3	mortality fecundity	0 no reduction
<i>O. laevigatus</i>	nymphs	Milbeknock 1% EC (leaves)	27.9	mortality fecundity	3 no reduction
<i>O. laevigatus</i>	nymphs	Milbeknock 1% EC (leaves)	34.8	mortality fecundity	0 29
<i>O. laevigatus</i>	nymphs	Milbeknock 1% EC (leaves)	5.394	mortality fecundity	5.5 -25
<i>O. laevigatus</i>	nymphs	Milbeknock 1% EC (leaves)	0.522	mortality fecundity	0 -23
<i>O. laevigatus</i>	nymphs	Milbeknock 1% EC (leaves)	3 x 30	mortality fecundity	0 -4
<i>O. laevigatus</i>	nymphs	Milbeknock 1% EC (leaves; 7-days aged residues)	34.8	mortality	0
<i>O. laevigatus</i>	nymphs	Milbeknock 1% EC (leaves; 7-days aged residues)	5.394	mortality	1.8
<i>O. laevigatus</i>	nymphs	Milbeknock 1% EC (leaves; 7-days aged residues)	0.522	mortality	9.2
<i>O. laevigatus</i>	nymphs	Milbeknock 1% EC (leaves; 7-days aged residues)	3 x 30	mortality	16.6

<i>C. septempunctata</i>	2 nd instar larvae	Milbeknock 1% EC	25 and 42	mortality	100
<i>A. rhopalosiphi</i>	adults	Milbeknock 1% EC	25 and 42	mortality	100
<i>A. rhopalosiphi</i>	adults	Milbeknock 1% EC (leaves)	9.3	mortality fecundity	4 no reduction
<i>A. rhopalosiphi</i>	adults	Milbeknock 1% EC (leaves)	27.9	mortality fecundity	10 12.5 (ns)
<i>A. rhopalosiphi</i>	adults	Milbeknock 1% EC (leaves)	34.8	mortality fecundity	6.7 2
<i>A. rhopalosiphi</i>	adults	Milbeknock 1% EC (leaves)	5.394	mortality fecundity	0 -21.8
<i>A. rhopalosiphi</i>	adults	Milbeknock 1% EC (leaves)	0.522	mortality fecundity	0 -17.8
<i>A. rhopalosiphi</i>	adults	Milbeknock 1% EC (leaves)	3 x 30	mortality fecundity	0 14.9
<i>A. rhopalosiphi</i>	adults	Milbeknock 1% EC (leaves, 7-days aged residue)	34.8	mortality	0
<i>A. rhopalosiphi</i>	adults	Milbeknock 1% EC (leaves, 7-days aged residue)	5.394	mortality	0
<i>A. rhopalosiphi</i>	adults	Milbeknock 1% EC (leaves, 7-days aged residue)	0.522	mortality	0
<i>A. rhopalosiphi</i>	adults	Milbeknock 1% EC (leaves, 7-days aged residue)	3 x 30	mortality	0
<i>P. cupreus</i>	adults	Milbeknock 1% EC	27.9	mortality feeding	no effect no effect

Earthworms

Acute toxicity:

Milbemectin: LC₅₀ 57 mg/kg dry soil (10% OM) equivalent to 28.5 mg/kg for a soil with the standard average organic matter content (5%), which is used for risk assessment.

27-hydroxy-milbemycin A₄: LC50 >500 mg/kg dry soil (10% OM) equivalent to >250 mg/kg for a soil with the standard average organic matter content (5%), which is used for risk assessment.

27-keto-milbemycin A₄: LC50 >1000 mg/kg dry soil (10% OM) equivalent to >500 mg/kg for a soil with the standard average organic matter content (5%), which is used for risk assessment.

Reproductive toxicity:

NOEC (reproduction) 21.72 mg product/kg dry soil (10% OM) equivalent to 0.217 mg as/kg dry soil (10% OM). Correction to the standard average organic matter content of 5% gives a NOEC of 0.109 mg as/kg dry soil, which is used for risk assessment.

Soil micro-organisms

Nitrogen mineralization:

Milbemectin: <25% effect after 28 d on nitrification at a dosage of 0.1 mg/kg, one soil was incubated too dry.

27-hydroxy- milbemycin A₄: <25% effect within 42 days on nitrification at a dosage of 0.1 mg/kg.

27-keto-milbemycin A₄: <25% effect within 42 days on nitrification at a dosage of 0.1 mg/kg.

Carbon mineralization:

Milbemectin: ~25% effect after 28 days in one of three examined soils at a dosage of 0.1 mg/kg, one soil was incubated too dry.

27-hydroxy- milbemycin A₄: <25% effect after 28 days at a dosage of 0.1 mg/kg.

27-keto-milbemycin A₄: <25% effect after 28 days at a dosage of 0.1 mg/kg.

APPENDIX III**MILBEMECTIN**

List of studies which were submitted during the evaluation process and were not cited in the draft assessment report:

B.1 Identity, B.2 Physical and chemical properties, B.3 Data on application and further information, B.4 Proposals for classification and labelling, B.5 Methods of analysis

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not
IIA, 4.2.1/08	Brice, A.	2003	Milbemectin and Metabolites: Validation of an Analytical Method for the confirmation of Residues in Crops Covance Laboratories.: 730/81 (Sankyo: To be allocated) GLP, Unpublished
IIA, 4.2.1/09	Wolf, S.	2003	Independent laboratory validation of the residue analytical method for Milbemycin A ₄ in apples (whole fruit) RCC Ltd: 847329 (Sankyo: To be allocated) GLP, Unpublished
IIA, 4.2.2/04	Croucher, A.	2002	Milbemectin and Metabolites: Validation of an Analytical Method for the confirmation of residues in Soil Covance Laboratories.: 730/72 (Sankyo: To be allocated) GLP, Unpublished
IIA, 4.2.3/04	Kendall, T.Z., Nixon, W.B., Glassbrook, N.	2003	A confirmatory method validation for the determination of milbemectin in freshwater and saltwater using liquid chromatography/ Mass spectrometry (LC/MS) Wildlife International Ltd.: 420C-107 (Amended report) (Sankyo: To be allocated) GLP, Unpublished
IIIA 5.1/01	Bates M.L.	2003	Milbeknock 1% EC: Validation of an Analytical Procedure for the determination of active ingredient in the formulation 730/103-D2149 GLP, not published

B.6 Toxicology and metabolism

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not
IIA, 5.8.1/01	Yamamoto, T. et al.	1990	Mouse Acute Oral Toxicity Study with Impurities and Metabolites of E-187. Sankyo Co., Ltd. Agricultural Chemicals Research Laboratories Report No. AB89-051 and AB90-028 Sankyo Agro Company, Ltd report Non-GLP, Unpublished
IIA, 5.8.1/02	Yamamoto, T. et al.	1989	Reverse Mutagenicity Study with Impurities and Metabolites of E-187. Sankyo Co., Ltd. Agricultural Chemicals Research Laboratories Report No. AB89-052 and AB89-057 Sankyo Agro Company, Ltd report Non-GLP, Unpublished
IIA, 5.8.1/03	Yamamoto, T. et al.	1989	DNA Repair Study with Impurities and Metabolites of E-187. Sankyo Co., Ltd. Agricultural Chemicals Research Laboratories Report No. AB89-052 and AB89-056 Sankyo Agro Company, Ltd report Non-GLP, Unpublished
IIA, 5.8.1/04	Williams, L.	2004	8,9Z-M.A ₃ : Reverse mutation in four histidine-requiring strains of <i>Salmonella typhimurium</i> and one tryptophan-requiring strain of <i>Escherichia coli</i> Covance Laboratories Ltd, UK Company report No.: MmT-TmG-007 Covance report No.: 730/106 GLP, Unpublished
IIA, 5.8.1/05	Williams, L.	2004	8,9Z-M.A ₄ : Reverse mutation in four histidine-requiring strains of <i>Salmonella typhimurium</i> and one tryptophan-requiring strain of <i>Escherichia coli</i> Covance Laboratories Ltd, UK Company report No.: MmT-TmG-008 Covance report No.: 730/109 GLP, Unpublished
IIA, 5.8.1/06	Whitwell, J.	2004	8,9Z-M.A ₃ : Induction of chromosome aberrations in cultured human peripheral blood lymphocytes Covance Laboratories Ltd, UK Company report No.: MmT-TmG-009 Covance report No.: 730/108 GLP, Unpublished
IIA, 5.8.1/07	Kumaravel, T.S.	2004	8,9Z-M.A ₄ : Induction of chromosome aberrations in cultured human peripheral blood lymphocytes Covance Laboratories Ltd, UK Company report No.: MmT-TmG-010 Covance report No.: 730/111 GLP, Unpublished

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not
IIA, 5.8.1/08	Lloyd, M.	2004	8,9Z-M.A ₃ : Mutation at the thymidine kinase (<i>tk</i>) locus of mouse lymphoma L5178Y cells (MLA) using the microtitre ^R fluctuation technique Covance Laboratories Ltd, UK Company report No.: MmT-TmG-011 Covance report No.: 730/107 GLP, Unpublished
IIA, 5.8.1/09	Lloyd, M.	2004	8,9Z-M.A ₄ : Mutation at the thymidine kinase (<i>tk</i>) locus of mouse lymphoma L5178Y cells (MLA) using the microtitre ^R fluctuation technique Covance Laboratories Ltd, UK Company report No.: MmT-TmG-012 Covance report No.: 730/110 GLP, Unpublished

B.7 Residue data

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not
IIA, 4.2.1/10	Dykeman, R.G.	1999	Determination of the Magnitude of Residues of Milbemectin in Apple RAC's from Trees Treated with a Milbeknock Emulsifiable Concentrate Formulation. Compliance Services International Report No. 97011 Sankyo Agro Company, Ltd report GLP, Unpublished

B.8 Environmental fate and behaviour

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not
IIA, 7.1.2/02	Brice, A.	2002	27-Keto-MA ₄ and 27-Hydroxy-MA ₄ : Adsorption/Desorption in Three Soils Covance Laboratories.: 730/71 (Sankyo: To be allocated) GLP, Unpublished

B.9 Ecotoxicology

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not
IIA, 8.2.1/05	Gries, T., V. Purghart and J. Runyon	2003	Milbemectin technical: Acute toxicity test with common carp (<i>Cyprinus carpio</i>) under flow-through conditions, Springborn Smithers Labs, Horn, Switzerland, Report no. 1009.007.170, September 18, 2003 GLP, unpublished
IIA, 8.4.1/02	Lührs, U.	2003	Acute Toxicity (14 Days) of 27-hydroxy-milbemycin A4 to the Earthworm <i>Eisenia fetida</i> in Artificial Soil IBACON.: 14981021 (Sankyo: To be allocated) GLP, Unpublished
IIA, 8.4.1/03	Lührs, U.	2003	Acute Toxicity (14 Days) of 27-keto-milbemycin A4 to the Earthworm <i>Eisenia fetida</i> in Artificial Soil IBACON.: 14991021 (Sankyo: To be allocated) GLP, Unpublished
IIA, 8.5/02	Reis, K. H.	2003	Effects of 27-hydroxy-milbemycin A4 on the Activity of the Soil Microflora in the Laboratory IBACON.: 14982080 (Sankyo: To be allocated) GLP, Unpublished
IIA, 8.5/03	Reis, K. H.	2003	Effects of 27-keto-milbemycin A4 on the Activity of the Soil Microflora in the Laboratory IBACON.: 14992080 (Sankyo: To be allocated) GLP, Unpublished
IIIA, 10.2.1/02	Gries, T. and V. Purghart	2003	Milbeknock EC (1.0%): Acute toxicity test with rainbow trout (<i>Oncorhynchus mykiss</i>) under static conditions in the presence of sediment, Springborn Smithers Labs, Horn, Switzerland, Report no. 1009.007.103, September 17, 2003 GLP, unpublished
IIIA, 10.2.1/03	Gries, T., V. Purghart and J. Runyon	2003	Milbeknock EC (1.0%): Acute toxicity test with rainbow trout (<i>Oncorhynchus mykiss</i>) under static conditions, Springborn Smithers Labs, Horn, Switzerland, Report no. 1009.008.103, September 17, 2003 GLP, unpublished
IIIA, 10.2.1/05	Gries, T., V. Purghart and J. Runyon	2003	Milbeknock EC (1.0%): Acute immobilisation test with daphnids (<i>Daphnia magna</i>) under static conditions in the presence of sediment, Springborn Smithers Labs, Horn, Switzerland, Report no. 1009.007.110, September 30, 2003 GLP, unpublished
IIIA, 10.2.1/06	Gries, T., V. Purghart and J. Runyon	2003	Milbeknock EC (1.0%): Acute immobilisation test with daphnids (<i>Daphnia magna</i>) under static conditions, Springborn Smithers Labs, Horn, Switzerland, Report no. 1009.008.110, September 30, 2003 GLP, unpublished

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not
IIIA, 10.2.1/07	Kroos, M.	2003	Evaluation of direct effects of Milbeknock EC (1%) on different aquatic organisms in a 72h-screening test, Covance Labs GmbH, Münster, Germany, Report no. 1873-0730-093, October 30, 2003 GLP, unpublished
IIIA, 10.2.1/08	Kroos, M.	2003	Evaluation of direct effects of Milbeknock EC (1%) on Ephemeroptera in a 48h-screening test, Covance Labs GmbH, Münster, Germany, Report no. 1893-0730-095, October 30, 2003 GLP, unpublished
IIIA, 10.2.1/09	Kroos, M.	2003	Evaluation of direct effects of Milbeknock EC (1%) on Chaoboridae in a 48h-screening test, Covance Labs GmbH, Münster, Germany, Report no. 1894-0730-096, October 30, 2003 GLP, unpublished
IIIA, 10.2.1/10	Kroos, M.	2003	Evaluation of direct effects of Milbeknock EC (1%) on Cladocera in a 48h-screening test, Covance Labs GmbH, Münster, Germany, Report no. 1895-0730-097, October 31, 2003 GLP, unpublished
IIIA, 10.2.1/11	Kroos, M.	2003	Evaluation of direct effects of Milbeknock EC (1%) on Copepoda in a 48h-screening test, Covance Labs GmbH, Münster, Germany, Report no. 1896-0730-098, October 31, 2003 GLP, unpublished
IIIA, 10.2.1/12	Kroos, M.	2003	Evaluation of direct effects of Milbeknock EC (1%) on Gastropoda (Planorbidae) in a 48h-screening test, Covance Labs GmbH, Münster, Germany, Report no. 1901-0730-099, October 31, 2003 GLP, unpublished
IIIA, 10.2.1/13	Kroos, M.	2003	Evaluation of direct effects of Milbeknock EC (1%) on Chironomidae in a 48h-screening test, Covance Labs GmbH, Münster, Germany, Report no. 1902-0730-100, October 31, 2003 GLP, unpublished
IIIA, 10.2.1/14	Kroos, M.	2003	Evaluation of direct effects of Milbeknock EC (1%) on Tubificidae in a 48h-screening test, Covance Labs GmbH, Münster, Germany, Report no. 1903-0730-101, October 31, 2003 GLP, unpublished
IIIA, 10.4.3/01	Schmitzer, S.	2004	The effects of Milbeknock 1 % EC on Honey bees (<i>Apis mellifera</i> L.) under semi-field (cage) conditions, IBACON, Rossdorf, Germany, Study no. 16071038, February 26, 2004 GLP, unpublished

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not
IIIA, 10.5.1/08	Vinall, S.	2002	Milbeknock 1% EC: an extended laboratory test to determine the effects of aged residues on the parasitic wasp, <i>Aphidius rhopalosiphi</i> , following treatment of apple trees Mambo-Tox Ltd. : SANK-01-1 (Sankyo: To be allocated) GLP, Unpublished
IIIA, 10.5.1/09	Vinall, S.	2002	Milbeknock 1% EC: an extended laboratory test to determine the effects of aged residues on the predatory mite, <i>Typhlodromus pyri</i> , following treatment of apple trees. Report No. SANK-01-2. GLP, Unpublished
IIIA, 10.5.1/10	Vinall, S.	2002	Milbeknock 1% EC: an extended laboratory test to determine the effects of aged residues on the foliar-active predator, <i>Orius laevigatus</i> , following treatment of apple trees. Report No. SANK-01-3. GLP, Unpublished
IIIA, 10.6.1.2/01	Lührs, U.	2002	Effects of Milbeknock 1% EC on reproduction and growth of earthworms, <i>Eisenia fetida</i> , in artificial soil. Study nr. 11861022. GLP, Unpublished

APPENDIX IV

List of uses supported by available data

Milbemectin

Crop and/or situation (a)	Member State or Country	Product name	F G or I (b)	Pests or Group of pests controlled (c)	Formulation		Application				Application rate per treatment			PHI (days) (l)	Remarks: (m)
					Type (d-f)	Conc. of as (i)	method kind (f-h)	growth stage & season (j)	number min max (k)	interval between applications (min)	kg as/ha min max	water l/ha min max	kg as/ha min max		
ornamentals	The Netherlands, Belgium, Spain, France, Germany, Italy	Milbeknock	G	Mites and leafminers	EC	9.3 g/l	high volume spraying (HVS), low volume spraying (LVS) on individual crops	full grown crops	2 – 10	7 d	0.00046 5 - 0.00093	500 – 3000	0.00233 - 0.0279	NA	blocks of 3 applications at 7 day intervals with a 4 week interval between blocks, up to a maximum of 9 applications per annum
Apples	Germany	Milbeknock	F	Mites	EC	9.3 g/l	Spraying	BBCH 69-76	2	60	0.00125	1000 - 1500	0.0125 – 0.0188	14	
Apples	France	Milbeknock	F	Mites	EC	9.3 g/l	Spraying	BBCH 69-72	1	10 - 21	0.00093 – 0.00116	400 - 1500	0.00372 – 0.0174	14	
Apples	Spain, Italy	Milbeknock	F	Mites	EC	9.3 g/l	Spraying	BBCH 69-85	2	10 - 21	0.00093 – 0.00116	400 - 1500	0.00372 – 0.0174	14	

Milbemectin

APPENDIX IV
List of uses supported by available data
04 April 2004

- Remarks:**
- (a) For crops, the EU and Codex classifications (both) should be used; where relevant, the use situation should be described (e.g. fumigation of a structure)
 - (b) Outdoor or field use (F), glasshouse application (G) or indoor application (I)
 - (c) e.g. biting and suckling insects, soil born insects, foliar fungi, weeds
 - (d) e.g. wettable powder (WP), emulsifiable concentrate (EC), granule (GR)
 - (e) GCPF Codes - GIFAP Technical Monograph No 2, 1989
 - (f) All abbreviations used must be explained
 - (g) Method, e.g. high volume spraying, low volume spraying, spreading, dusting, drench
 - (h) Kind, e.g. overall, broadcast, aerial spraying, row, individual plant, between the plants - type of equipment used must be indicated
 - (i) g/kg or g/l
 - (j) Growth stage at last treatment (BBCH Monograph, Growth Stages of Plants, 1997, Blackwell, ISBN 3-8263-3152-4), including where relevant, information on season at time of application
 - (k) The minimum and maximum number of application possible under practical conditions of use must be provided
 - (l) PHI - minimum pre-harvest interval
 - (m) Remarks may include: Extent of use/economic importance/restrictions