Abamectin

Document IIIA

Section 1: Applicant

From
Tier I - Section 1 - Annex II
of 91/414 dossier :
Identity, chemistry data and general information

Document IIIA – BPD 98/8	Section 1	APPLICANT
91/414 Annex Point addressed	II 1	Identity of the Active Substance

Section A1 Subsection (Annex Point)	Applicant		
1.1 Applicant (IIA I.1.1)	Name : Address : Contact name: Telephone: Fax number: E-mail address :	Syngenta European Centre Priestley Road – GU2 7YH Guildford - UK [redacted] [redacted] [redacted]	Official use only
1.2 Manufacturer of Active Substance (IIA I.1.2) (if different)	Name: Address: Contact person: Telephone: Fax number: E-mail address: Location of manufacturing plant: [redacted] Location of future manufacturing plant: [redacted]	Syngenta Crop Protection AG 4002 Basel Switzerland [redacted] [redacted]	

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	16 June 2008
Materials and Methods	[redacted]
Results and discussion	-
Conclusion	-
Reliability	-
Acceptability	[redacted]
Remarks	
	COMMENTS FROM ...
Date	
Materials and Methods	
Results and discussion	
Conclusion	
Reliability	
Acceptability	
Remarks	

Abamectin

Document IIIA

Section 2: Identity

From
Tier I - Section 1 - Annex II
of 91/414 dossier :
Identity, chemistry data and general information

Document IIIA – BPD Section 2 IDENTITY 98/8

2.1 Common name : Abamectin

Official use only

2.2 Chemical name :

IUPAC nomenclature :

Avermectin B_{1a}

(10E, 14E, 16E, 22Z)-(1R,4S,5'S,6S,6'R,8R,12S,13S,20R,21R,24S)-6'[(S)-sec-butyl]-21,24-dihydroxy-5',11,13,22-tetramethyl-2-oxo-3,7,19-trioxatetracyclo[15.6.1.$1^{4,8}$.$O^{20,24}$] pentacosa-10,14,16,22-tetraene-6-spiro-2'-(5'6'-dihydro-2'H-pyran)-12-yl 2,6-dideoxy-4-O-(2,6-dideoxy-3-O-methyl-α-L-*arabino*-hexopyranosyl)-3-O-methyl-α-L-*arabino*-hexopyranoside

Avermectin B_{1b}

(10E, 14E, 16E, 22Z)(1R,4S,5'S,6S,6'R,8R,12S,13S,20R,21R,24S)-21,24-dihydroxy-6'isopropyl-5',11,13,22-tetramethyl-2-oxo-3,7,19-trioxatetra-cyclo[15.6.1.$1^{4,8}$.$O^{20,24}$] pentacosa-10,14,16,22-tetraene-6-spiro-2'-(5',6'-dihydro-2'H-pyran)-12-yl 2,6-dideoxy-4-O-[2,6-dideoxy-3-O-methyl-α-L-*arabino*-hexopyranosyl)-3-O-methyl-α-L-*arabino*-hexapyranoside

CA nomenclature :

Abamectin

avermectin B1

avermectin B_{1a}

5-O-demethyl-avermectin A_{1a}

Official use only

avermectin B_{1b}

5-O-demethyl-25-de(1-methylpropyl)-25-(1-methylethyl)-avermectin A_{1a}

2.3 Syngenta code number :

MK 936	(abamectin)
NOA 422601	(avermectin B_{1a})
NOA 421704	(avermectin B_{1b})

Official use only

2.4 CAS and EC numbers

2.4.1 **CAS number :** 71751-41-2 (abamectin)
65195-55-3 (avermectin B_{1a})
65195-56-4 (avermectin B_{1b})

2.4.2 **EINECS number** : 265-610-3 (avermectin B_{1a})
265-611-9 (avermectin B_{1b})

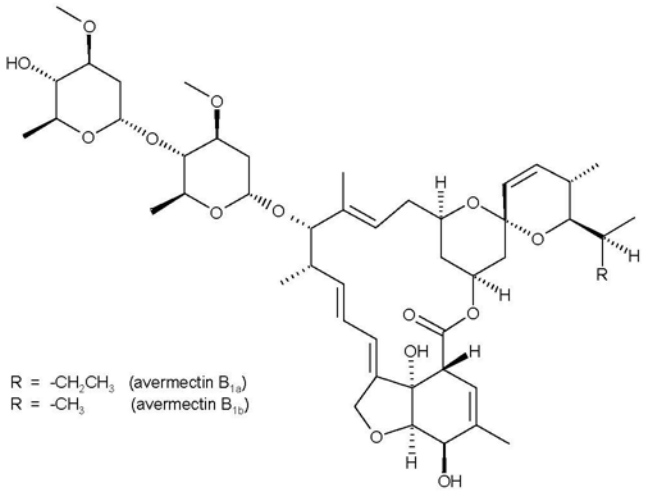
Official use only

2.4.3 **CIPAC number :** 495 (abamectin)

2.5 Molecular and structural formula, molecular mass

2.5.1 **Molecular formula** : $C_{48}H_{72}O_{14}$ (avermectin B_{1a})
$C_{47}H_{70}O_{14}$ (avermectin B_{1b})

2.5.2 **Structural formula :**



Official use only

2.5.3 **Molecular mass :** 873.1(avermectin B_{1a})
859.1(avermectin B_{1b})

2.6 Method of manufacture of active substance:

Official use only

CONFIDENTIAL – data provided in separate confidential document

2.7 Specification of purity of the active substance as appropriate

Minimum purity of the active substance is 900 g/kg.

Official use only

Identity of impurities and additives, as appropriate

CONFIDENTIAL – data provided in separate confidential document

2.8 Origin of the natural active substance or the precursor(s) of the active substance

Abamectin is a naturally occurring macrocyclic lactone produced by the actinomycete *Streptomyces avermetilis*.

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	November 2008
Materials and Methods	[redacted]
Results and discussion	
Conclusion	[redacted]
Reliability	
Acceptability	
Remarks	
	COMMENTS FROM ...
Date	
Materials and Methods	
Results and discussion	
Conclusion	
Reliability	
Acceptability	
Remarks	

Section A2.10
Annex Point IIA2.10

Exposure data in conformity with Annex VIIA to Council Directive 92/32/EEC (OJ No L, 05.06.1992, p. 1) amending Council Directive 67/548/EEC

Subsection		Official use only
2.10.1	**Human exposure towards active substance**	
2.10.1.1	**Production**	
	Production of the active ingredient	
	i) Description of process	Abamectin is produced by fermentation, followed by isolation and purification *Details of the manufacturing process can be found in the confidential information.*
	ii) Workplace description	[redacted] Abamectin is generally handled in dedicated, enclosed systems, with typical exposure times of no more than 30 minutes per campaign ([redacted]).
	iii) Inhalation exposure	Syngenta has established a recommended airborne occupational exposure limit (OEL) for abamectin of 0.02 mg/m^3, as an 8-hour time-weighted average. This limit is set to prevent signs of toxicity due to inhalation of abamectin dust. Syngenta's experience in a number of formulation operations shows that exposure during container opening and material transfers can be successfully controlled below the OEL by the use of enclosed or semi-enclosed exhaust ventilated work stations or ventilated glove boxes. Work enclosures, containments and ventilation systems should be designed and operated to keep employee exposures to airborne abamectin dust below the OEL. Where this is not possible, appropriate respiratory protection and protective clothing should be used to protect workers from overexposure.
	iv) Dermal exposure	Direct dermal contact with abamectin is not foreseen. An incidental contact is possible during transfer of the substance to the mixing vessel. Protective equipment for the mixing process; see workplace description.

Section A2.10 Annex Point IIA2.10	Exposure data in conformity with Annex VIIA to Council Directive 92/32/EEC (OJ No L, 05.06.1992, p. 1) amending Council Directive 67/548/EEC

As a routine practice, abamectin workers should remove their street clothes and put on protective coveralls, gloves, eye protection and foot protection prior to entry into the restricted area. The degree of protection will vary depending on the nature of the work and the engineering controls that are used to control potential employee contact.
Upon exiting the work area, workers should carefully remove their protective clothing, taking care to avoid contact with contaminated items. Protective clothing and equipment should be placed in special covered containers to await cleaning or disposal. Workers should immediately wash their hands and face, and then take a shower as soon as it is practical (preferable, before donning their street clothes).

Production of the formulations

i) Description of process

See also documents Doc III-B1 Section 2.10.doc, Doc III-B2 Section 2.10.doc, Doc III-B3 Section 2.10.doc

Raid Ant Bait and Raid Roach Bait:

[redacted]

Avert Dry Flowable Cockroach Bait:

[redacted]

ii) Workplace description

Raid Ant Bait and Raid Roach Bait:

- PREMIX PRODUCTION
  A glove box and a hood with suction system will be installed inside the storage area.
  Abamectin powder will be moved from the locked storage into the glove box.
  Once the box is sealed, a stainless steel hopper will be fed through a pipe with an approximate known quantity of peanut oil. An approximate quantity of abamectin will be fed into the hopper and mixed until dissolution to obtain a premix with [redacted] y providing abamectin [redacted] the pre-mix manufacturer can use only one whole package of abamectin that, once removed from the glove box, can be removed directly to waste storage.
- TRANSFER OF PREMIX TO THE MAIN MIXER
  The correct amount of premix will be fed into the small

Section A2.10
Annex Point IIA2.10

Exposure data in conformity with Annex VIIA to Council Directive 92/32/EEC (OJ No L, 05.06.1992, p. 1) amending Council Directive 67/548/EEC

closed stainless steel hopper on the balance. [redacted] The other raw materials will then be loaded to complete the formula

Avert Dry Flowable Cockroach Bait:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

iii) Inhalation exposure

Raid Ant Bait and Raid Roach Bait:
The manufacturing process is both highly mechanised and highly controlled to prevent exposure via oral, dermal or inhalation routes of plant personnel during manufacture
Avert Dry Flowable Cockroach Bait:
Appropriate LEV and PPE is utilised at each stage of the production process. This prevents exposure by the inhalation route.

iv) Dermal exposure

Raid Ant Bait and Raid Roach Bait:
The manufacturing process is both highly mechanised and highly controlled to prevent exposure via oral, dermal or inhalation routes of plant personnel during manufacture
Avert Dry Flowable Cockroach Bait:
Appropriate LEV and PPE is utilised at each stage of the production process. This prevents exposure by the dermal route.

Section A2.10 Annex Point IIA2.10	Exposure data in conformity with Annex VIIA to Council Directive 92/32/EEC (OJ No L, 05.06.1992, p. 1) amending Council Directive 67/548/EEC

2.10.1.2 Intended use(s)

1. Professional Users **Raid Ant Bait and Raid Roach Bait:**	not intended for use by professional users
Avert Dry Flowable Cockroach Bait:	
i) Description of application process	Avert Dry Flowable Cockroach Bait 310A is supplied in a small, 30g, hand-held puffer pack. It is intended that this pack is used to directly apply the product as discrete bait points into cracks and crevices throughout an infested area.
ii) Workplace description	Not relevant for an insecticide as the 'workplace' is each infested treatment site. Although the nature of the treatment sites will vary, the tasks undertaken when using an insecticidal bait are the same.
iii) Inhalation exposure	Given the manner of use of the product, the situations in which it will be used, the recommended locations for application, e.g. cracks and crevices, and the relatively large particle size (refer B3.11_01), negligible inhalation exposure is expected (refer B6.1.3_02).
iv) Dermal exposure	Given the manner of use of the product, the situations in which it will be used, the recommended locations for application, e.g. cracks and crevices, and the relatively large particle size (refer B3.11_01), negligible dermal exposure is expected (refer B6.1.3_02). Furthermore, given the situations in which cockroach infestations occur, it would be expected that Operators wear gloves to protect against disease transmission.
2. Non-professional Users including the general public **Avert Dry Flowable Cockroach Bait:**	Product is only for sale to industrial/professional users
Raid Ant Bait and Raid Roach Bait:	

Section A2.10 Annex Point IIA2.10	Exposure data in conformity with Annex VIIA to Council Directive 92/32/EEC (OJ No L, 05.06.1992, p. 1) amending Council Directive 67/548/EEC
i) Description of application process	Applications are made inside and around buildings including domestic properties. The bait stations are designed to prevent exposure during opening the packaging or during placing of the stations. The bait stations are closed boxes made of plastic with pre-formed access holes so that the user does not need to puncture the bait station and thereby avoids any dermal contact with the product. They are positioned in places where the insects walk. The insects take the product out of the bait station and back to their nest, so that they die in the nest. Since it may take several days before the whole nest is wiped out, the bait stations should remain in the same place for at least one week. **Raid Ant Bait:** The recommended bait station frequency is 2 per small room (12 m^2). The bait is expected to remain effective for up to three months, although the entire contents may be removed by the pest earlier. One bait station contains approximately 1.5 g of product. Disposal of the used bait station is to domestic waste. Ant bait stations are intended for indoor use and for outdoor use (e.g. on balconies and patios) around perimeter walls within the drip line of buildings. **Raid Roach Bait:** The recommended bait station frequency is 4 per small room (12 m^2). The bait is expected to remain effective for up to three months, although the entire contents may be removed by the pest earlier. One roach bait station contains approximately 2.5 g of product. Disposal of the used bait station is to domestic waste. Roach bait stations are intended for indoor use only.
ii) Workplace description	According to EU Guidance document report 2002 Part II, Point 6.1 relating to evaporation from ant and cockroach bait stations "evaporation of these substances will be so small that the inhalation exposure is considered to be negligible". Furthermore, 'Raid Ant Bait' is contained inside a plastic sealed box and abamectin has a very low vapour pressure (<3.7×10^{-6} Pa at 25°C). Thus, the potential exposure of users is negligible and can be discounted.

Section A2.10
Annex Point IIA2.10

Exposure data in conformity with Annex VIIA to Council Directive 92/32/EEC (OJ No L, 05.06.1992, p. 1) amending Council Directive 67/548/EEC

iii) Inhalation exposure	In an acute dermal toxicity study the no effect level was greater than 2000 mg/kg bw in rabbits. Therefore, there is also an adequate margin of safety for potential dermal exposure
iv) Dermal exposure	Not applicable
2.10.2 Environmental exposure towards active substance	[redacted] The whole package is finally put into a 10 US gallon plastic drum fitted with a screw cap. Abamectin is generally handled in dedicated, enclosed systems.
2.10.2.1 Production of the formulation	
(i) Releases into water	The formulation is produced in a closed system; therefore no releases into water occur during production.
(ii) Releases into air	The formulation is produced in a closed system; therefore no releases into air occur during production.
(iii) Waste disposal **Raid Ant Bait and Raid Roach Bait:**	The hopper is discharged into the mixer, already charged with remaining peanut oil. WASTE STORAGE Inside the raw material storage area a sealed container will be dedicated for waste storage. No waste materials are produced during the production process.
Avert Dry Flowable:	
2.10.2.2 Intended use(s)	see Doc. II-B
Affected compartment(s):	see Doc. II-B
water	see Doc. II-B
sediment	see Doc. II-B
air	see Doc. II-B
soil	see Doc. II-B
Predicted concentration in the affected compartment(s)	see Doc. II-B
water	see Doc. II-B
sediment	see Doc. II-B
air	see Doc. II-B
soil	see Doc. II-B

Section A2.10
Annex Point IIA2.10

Exposure data in conformity with Annex VIIA to Council Directive 92/32/EEC (OJ No L, 05.06.1992, p. 1) amending Council Directive 67/548/EEC

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	16 June 2008, IIIA 2.10 (Exposure data)
Materials and Methods	[redacted]

	[redacted]
Results and discussion	
Conclusion	[redacted]
Reliability	-
Acceptability	[redacted]
Remarks	[redacted]
	COMMENTS FROM ...
Date	
Materials and Methods	
Results and discussion	
Conclusion	
Reliability	
Acceptability	
Remarks	

Abamectin

Document IIIA

Section 3: Physical & Chemical Properties

From
Tier I - Section 1 - Annex II
of 91/414 dossier :
Identity, chemistry data and general information

Document IIIA – BPD 98/8	Section 3	PHYSICAL AND CHEMICAL PROPERTIES						
91/414 Annex Point addressed	II 2	Physical and Chemical Properties of the Active Substance						
Section A3	**Physical and chemical properties of active substance**							
Subsection (Annex Point)	**Method**	**Purity/ Specification**	**Results**	**Remarks/ Justification**	**GLP (Y/N)**	**Reliability**	**Reference**	**Official use only**
3.1 Melting point, boiling point, relative density (IIA III.3.1)								
3.1.1 Melting point	OECD 102 (capillary method)	[redacted]	**Melting range: 161.8 °C – 169.4 °C, with thermal decomposition during melting.**	-	Y	1	A 3.1.1(1) Das, R. 1999a	
3.1.2 Boiling point	-	-	**Not determined; the substance decomposes before a boiling point is reached (see Melting point).**		-	-	-	
Temperature of decomposition or sublimation			**Decomposition starts at about 162 oC (see Melting point).**				Das, R. (1999a)	
3.1.3 Bulk density/ relative density	OECD 109 Air comparison pycnometer method	[redacted]	**Density 1.18 x 103 kg/m3 at 22°C, corresponding to a relative density of 1.18**	-	Y No temperature stated	1	A 3.1.3(1) Füldner, H.H. 1999	
3.2 Vapour pressure (IIA III.3.2)	OECD 104 (gas saturation method)	[redacted]	**Vapour pressure of abamectin in the solid state < 3.7 x 10-6 Pa at 25 oC was calculated using the LOQ of the test substance.**		Y	1	A 3.2(1) Widmer, H. 1999	

Document IIIA – BPD 98/8	Section 3	PHYSICAL AND CHEMICAL PROPERTIES
91/414 Annex Point addressed	II 2	Physical and Chemical Properties of the Active Substance

Section A3	Physical and chemical properties of active substance							
Subsection (Annex Point)	**Method**	**Purity/ Specification**	**Results**	**Remarks/ Justification**	**GLP (Y/N)**	**Reliability**	**Reference**	**Official use only**
3.2.1 Henry's Law Constant (IIA III.3.2)	Calculation	-	**< 2.7 x 10-3 Pa.m3/mol at 25°C :**	-	-	-	A 3.2.1(1) Burkhard, N. 1999	
3.3 Appearance (IIA III.3.3)								
3.3.1 Physical state	Visual observation	[redacted]	**Powder (25°C)**	-	Y	1	A 3.3(1) Das, R. 1999b	
3.3.2 Colour			**White (25°C)**					
3.3.3 Odour				The odour of the substance was not determined.	Acceptable as this is a dangerous exercise			
3.4 Absorption spectra (IIA III.3.4)		Abamectin Technical [redacted]		-	Y	1	A 3.4(1) Oggenfuss, P. 1999	
Spectra	OECD 101 (UV/VIS)	Purity unknown (TAI)	UV-VIS : no maximum above 290nm. Acceptable ^{1}H-NMR, ^{13}C-NMR, IR and MS spectra were submitted.		Y		Oggenfuss, P. (1999)	

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91/414 Annex Point addressed	II 2	Physical and Chemical Properties of the Active Substance

Section A3	Physical and chemical properties of active substance							
Subsection (Annex Point)	**Method**	**Purity/ Specification**	**Results**	**Remarks/ Justification**	**GLP (Y/N)**	**Reliability**	**Reference**	**Official use only**
UV/VIS	Methanol solution		**The molar extinction coefficients were determined to be:** **pH λ ext. coeff.** **neutral 245 32549** **255 18983** **acidic 245 34515** **255 20977** **basic 245 29551** **No absorption maximum between 280 nm and 750 nm was observed.**	-	Y	1	A 3.4(1) Oggenfuss, P. 1999	
IR	KBr pellet		**Spectra consistent with complex structure**	-	Y	1	A 3.4(1) Oggenfuss, P. 1999	
NMR	^{1}H-NMR (500 MHz, $CDCl_3$) ^{13}C-NMR (125 MHZ, $CDCl_3$)		**Spectra consistent with complex structure**	-	Y	1	A 3.4(1) Oggenfuss, P. 1999	

Document IIIA – BPD 98/8	Section 3	PHYSICAL AND CHEMICAL PROPERTIES
91/414 Annex Point addressed	II 2	Physical and Chemical Properties of the Active Substance

Section A3	Physical and chemical properties of active substance							
Subsection (Annex Point)	**Method**	**Purity/ Specification**	**Results**	**Remarks/ Justification**	**GLP (Y/N)**	**Reliability**	**Reference**	**Official use only**
MS	(neg. APCl)		**Spectra consistent with complex structure**	-	Y	1	A 3.4(1) Oggenfuss, P. 1999	
3.5 Solubility in water (IIA III.3.5)	*including effects of pH (5-9)*							
Solubility in water	OECD 105 (shake flask method) Based on EEC A6	Purity unknown (TAI)	**Water solubility was 1.21 ± 0.15 mg/L at 25°C (pH is 7.57±0.23)**	. GLP, although the measured value is lower than 10 mg/L, which is the limit for the shake flask method according to OECD 105, it is considered acceptable.	Y	1	A 3.5(1) McCauley, J.A. 1997	
3.6 Dissociation constant (-)(pK_a)	OECD guideline 112 (spectrophotometric titration)	[redacted]	**No dissociation or spectral changes were observed in the 1-12 pH range.**	GLP, Only 4 pH values were tested, which is considered acceptable because the test substance did not dissociate.	Y	1	A 3.6(1) Hörmann, A. 1999	

Document IIIA – BPD 98/8	Section 3	PHYSICAL AND CHEMICAL PROPERTIES
91/414 Annex II Point addressed 2	Physical and Chemical Properties of the Active Substance	

Section A3	Physical and chemical properties of active substance							
Subsection (Annex Point)	**Method**	**Purity/ Specification**	**Results**	**Remarks/ Justification**	**GLP (Y/N)**	**Reliability**	**Reference**	**Official use only**
3.7 Solubility in organic solvents (technical active substance) including the effect of temperature on solubility (IIIA-III.1)	Similar to CIPAC method MT157.3	[redacted]	**Solvent / Solubility g/L** **Acetone: 72** **Dichloromethane: 470** **Ethyl acetate: 160** **Hexane: 0.110** **Methanol: 13** **Octanol: 83** **Toluene: 23**	-	Y GLP,The notifier to explain the difference found in solubility of abamectine in toluene compared to the value stated in the e-Pesticide manual (350 g/l).	1	A 3.7(1) Stulz, J. 1999	
3.8 Stability in organic solvents used in b.p. and identity of relevant breakdown products (IIIA-III.2)	Not applicable because active substance is not formulated in solvent solution.							

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91/414 Annex Point addressed	II 2	Physical and Chemical Properties of the Active Substance

Section A3	Physical and chemical properties of active substance							
Subsection (Annex Point)	**Method**	**Purity/ Specification**	**Results**	**Remarks/ Justification**	**GLP (Y/N)**	**Reliability**	**Reference**	**Official use only**
3.9 Partition coefficient n-octanol/water (IIA III.3.6)	*including effects of pH (5-9)*							
Partition co-efficient (log Pow 1)	Based on EC method (shake flask method)	[redacted]	**l Average logKow was 4.4 ± 0.3 (room temperature, pH 7.2) Estimated LogKOW using the KOWWIN program (v.1.66) is 4.48 (for Avermectin B1a)**		Y GLP, Although abamectine is a surface active substance and the shake flask method is usually not suitable for high logKow values, the study is found acceptable, because the found value is comparable with the values found in literature and KOWWIN calculations.	1	A 3.9(1) McCauley, J.A. 1996	

Document IIIA – BPD 98/8	Section 3	PHYSICAL AND CHEMICAL PROPERTIES
91/414 Annex II Point addressed 2	Physical and Chemical Properties of the Active Substance	

Section A3	Physical and chemical properties of active substance							
Subsection (Annex Point)	**Method**	**Purity/ Specification**	**Results**	**Remarks/ Justification**	**GLP (Y/N)**	**Reliability**	**Reference**	**Official use only**
3.10 Thermal stability, identity of relevant breakdown products (IIA III.3.7)	OECD 102	Abamectin Technical [redacted]	**Decomposes above melting point of 161.8°C - 169.4°C.**	Combustion products are likely to be oxides of carbon and water. Dangerous combustion products are unlikely.	Y	1	A 3.10(1) Das, R. 1999a	
3.11 Flammability and auto-flammability (technical active substance) (IIA III.3.8)								
	Directive 92/69/EEC, Part A.10 (flammability) and Part A.16 (auto flammability) EEC A16	[redacted]	**The substance is not highly flammable.**	-	Y	1	A 3.11(1) Angly, H. 1999a	
			No self-ignition was observed before melting point	-	Y	1	A 3.11(2) Angly, H. 1999b	
3.12 Flash point (technical active substance) (IIA III.3.9)	Not required. Abamectin is a solid with a melting point > 40 °C							

Document IIIA – BPD 98/8	Section 3	PHYSICAL AND CHEMICAL PROPERTIES
91/414 Annex II Point addressed 2	Physical and Chemical Properties of the Active Substance	

Section A3	Physical and chemical properties of active substance							
Subsection (Annex Point)	**Method**	**Purity/ Specification**	**Results**	**Remarks/ Justification**	**GLP (Y/N)**	**Reliability**	**Reference**	**Official use only**
3.13 Surface tension (IIA III.3.10)	OECD Guideline 115 Directive 92/69/EEC A.5 Wilhelmy plate method	[redacted]	**The averaged end values gave a surface tension of 52.4 mN/m at 90% of the saturation concentration at 20°C. Therefore, abamectin is considered a surface active substance (surface tension < 60 mN/m).**		Y	1	A 3.13(1) Martin, N. 1999	
3.14 Viscosity (-)	Not applicable because Abamectin is not a liquid.							
3.15 Explosive properties (technical active substance) (IIA III.3.11)	Directive 92/69/EEC, Part A.14	[redacted]	**The substance was considered not thermally, shock or friction sensitive.**	-	Y	1	A 3.15(1) Angly, H. 1999c	
3.16 Oxidising properties (technical active substance) (IIA III.3.12)	Directive 92/69/EEC, Part A.17	[redacted]	**No oxidizing properties**	-	Y	1	A 3.16(1) Angly, H. 1999d	
3.17 Reactivity towards container material (IIA III.3.13)	-	-	-	There is no record of any reaction to the container material	-	-	-	

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91/414 Annex Point addressed	II 2	Physical and Chemical Properties of the Active Substance

Section A3	Physical and chemical properties of active substance							
Subsection (Annex Point)	**Method**	**Purity/ Specification**	**Results**	**Remarks/ Justification**	**GLP (Y/N)**	**Reliability**	**Reference**	**Official use only**
IIIA 7.1.1.1.1 Stability in water **(IIA VII 7.6.2.1)**	US-EPA Subdivision N, 161-1, proposal 1982	[redacted]	No hydrolysis takes place at pH 5.6, 6.8 and 8.6 at 25 °C.	No significant hydrolysis of avermectin B_{1a} was observed.	No GLP	1	Maynard, S. and Ku, C.C. (1982)	

Document IIIA – BPD 98/8	Section 3	PHYSICAL AND CHEMICAL PROPERTIES
91/414 Annex Point addressed	II 2	Physical and Chemical Properties of the Active Substance

Section A3	Physical and chemical properties of active substance							
Subsection (Annex Point)	**Method**	**Purity/ Specification**	**Results**	**Remarks/ Justification**	**GLP (Y/N)**	**Reliability**	**Reference**	**Official use only**
IIIA 7.1.1.1.1 Hydrolysis rate **(IIA VII 7.6.2.1)**	US-EPA Subdivision N, 161-1, proposal 1982	[redacted] radio-chemical purity [5-^{3}H]-avermectin B1a. [23-^{14}C]-avermectin B1a, radiochemical purity [redacted]	No hydrolysis at pH 4 - 9, 25 °C	No significant hydrolysis of avermectin B_{1a} was observed.	No GLP	1	Maynard, S. and Ku, C.C. (1982)	
	OECD 111; US-EPA Subdivision N, 540/09-82-021, section 161-1 BBA 55, I and II		No hydrolysis at pH 4 - 7, 50 °C pH 9, 60 °C: 4.9 d pH 9, 50 °C: 9.9 d pH 9, 25 °C: 213 d (extrapolated) pH 9, 20 °C: 380 d (calculated with Arrhenius equation) metabolites: 2-epi-avermectin B1a: 25 % of AR at 50 and 60 °C 1,18 hydrolysed avermectin B1a: 17.5 % of AR at 60 °C unknown: 15.6 % of AR at 60 °C	Avermectin B_{1a} is considered to be hydrolytically stable under environmentally relevant temperatures and pHs.	GLP	1	Ellgehausen, H. (2001)	

Document IIIA – BPD 98/8	Section 3	PHYSICAL AND CHEMICAL PROPERTIES
91/414 Annex Point addressed	II 2	Physical and Chemical Properties of the Active Substance

Section A3	Physical and chemical properties of active substance							
Subsection (Annex Point)	**Method**	**Purity/ Specification**	**Results**	**Remarks/ Justification**	**GLP (Y/N)**	**Reliability**	**Reference**	**Official use only**
IIIA 7.1.1.1.2 Photochemical degradation **(IIA VII 7.6.2.2)**	US-EPA Subdivision N, 161 - 2 EPA 540/09-90-078	[23-^{14}C]-avermectin B1a, radiochemical purity [redacted]	Xenon lamp. DT_{50}: 2 d (equivalent to 1.5 sunlight days at 30-50 °N, pH 7) metabolites: NOA 448111: 5.6 % of AR [8,9-Z]-avermectin B_{1a}: 8.2 % of AR, $DT_{50,photo}$ 5.8 sunlight days at 30 - 50 °N	Photolysis of Avermectin B_{1a} in water represents a significant degradation process for the test substance.	GLP	1	Adam, D. (2001)	
Quantum yield	US-EPA Vol. 50, 188 (1985)	[5-^{3}H]-avermectin B_{1a}, radiochemical purity [redacted]	0.0347 (summer)		GLP	1	Halley, B.A. (1991)	
IIIA 7.3.1 Stability in air, photochemical oxidative degradation	Atkinson calculation (Atmospheric Oxidation program V1.82)	N/A	The overall OH rate constant was 629 x 10^{-12} cm^3/molecule.s, the DT_{50} was 12.2 minutes. The overall ozone rate constant was 121 x 10^{-17} cm^3/molecule.s, the DT_{50} was 13.6 minutes. The estimated half-life of abamectin is < 1 hour.	The estimated atmospheric half-life of abamectin by hydroxyl radicals or ozone reaction is therefore significantly less than one hour. The result $DT_{50,air}$ < 1 hour is used for risk assessment.	N/A	1	Stamm, E. (1998)	

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	30 January 2009
	IIIA 3.4 Absorption spectra
Materials and Methods	[redacted]
Results and discussion	-
Conclusion	[redacted]
Reliability	-
Acceptability	[redacted]
Remarks	-
	COMMENTS FROM ...
Date	
Materials and Methods	
Results and discussion	
Conclusion	
Reliability	
Acceptability	
Remarks	

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	14 December 2007
	IIIA 3.7 Solubility in organic solvents
Materials and Methods	[redacted]
Results and discussion	-
Conclusion	-
Reliability	-
Acceptability	[redacted]
Remarks	-
	COMMENTS FROM ...
Date	
Materials and Methods	
Results and discussion	
Conclusion	
Reliability	
Acceptability	
Remarks	

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	28 May 2008 IIIA 3.17 Reactivity towards container material
Materials and Methods	[redacted]
Results and discussion	
Conclusion	[redacted]
Reliability	
Acceptability	[redacted]
Remarks	
	COMMENTS FROM ...
Date	
Materials and Methods	
Results and discussion	
Conclusion	
Reliability	
Acceptability	
Remarks	

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	3 December 2007 Sections on stability in water, hydrolysis rate, photochemical degradation, quantum yield, stability in air, photochemical oxidative degradation
Materials and Methods	
Results and discussion	
Conclusion	
Reliability	
Acceptability	[redacted]
Remarks	
	COMMENTS FROM ...
Date	
Materials and Methods	
Results and discussion	
Conclusion	
Reliability	
Acceptability	
Remarks	

Abamectin

Document IIIA

Section 4: Analytical Methods for Detection and Identification

From
Tier I - Section 2 - Annex II
of 91/414 dossier:
Analytical Methods

4.1 Analytical methods for the determination of pure active substance and, where appropriate, for relevant degradation products, isomers and impurities of active substances and their additives (e.g. stabilisers)

98/8 Doc IIIA section No.	**4.1/ 01**	**Analytical methods for the determination of pure active substance and, where appropriate, for relevant degradation products, isomers and impurities of active substances and their additives (e.g. stabilisers)**
91/414 Annex Point addressed	**IIA 4.1**	**Analytical methods for determination of active substance**

Title of the Study:	**Abamectin technical - Content by HPLC**	**For official use only**
Dossier Reference:	4.1/01	
Method number: Author:	AW-211/2 (MK936/0634) Arenas, R.V	
Name and address of testing facility:	Novartis Crop Protection Inc., Greensboro, United States	
Test substance:	Abamectin technical	
Date of issue:	1999a	
Compliance with GLP:	No, but complies with sound scientific principles	
Reliability indicator	1	

For the study summary see Document IIIA reference point 4.1/02.

98/8 Doc IIIA section No.	**4.1/02**	**Analytical methods for the determination of pure active substance and, where appropriate, for relevant degradation products, isomers and impurities of active substances and their additives (e.g. stabilisers)**
91/414 Annex Point addressed	**IIA 4.1**	**Analytical methods for determination of active substance**

Title of the Study:	**Validation of analytical method AW-211/2 for the determination of abamectin in abamectin technical by HPLC**	**For official use only**
Dossier Reference:	4.1/02	
Method number: Author:	ASGSR-99-295 (MK936/0633) Arenas, R.V.	
Name and address of testing facility:	Novartis Crop Protection Inc., Greensboro, United States	
Test substance:	Abamectin	
Date of issue:	1999b	
Compliance with GLP:	Yes	
Reliability indicator	1	

Reference/notifier	:	Arenas, R.V. (1999a; analytical method) Arenas, R.V. (1999b; validation)	GLP statement	:	yes (validation study)
Type of study	:	analytical method technical substance with validation	Guideline	:	not applicable
Year of execution	:	1999	Acceptability	:	acceptable
Test substance	:	abamectin technical, batch EDS-163			

Description

Analysis method AW-211/2

Identification. The identity of the test compound can be determined by IR spectroscopy, Mass Spectoscopy (MS) or liquid chromatography (HPLC). IR-spectroscopy: KBr pellet technique. The IR-spectrum is recorded in the range 4000 - 600 cm^{-1}, and is qualitatively compared with that of abamectin. MS: The identity of the test compound can be established by confirmation of the molecular structure using fragmentation pattern or comparison of fragmentation pattern to a known standard. HPLC: The test substance can be identified by comparison with retention times of known standards.

Determination of content. Avermectin B_{1a} and B_{1b} are determined separately by LC with external standards. The sum is calculated and reported as abamectin. Column: Zorbax ODS, particle size 5 µm, column length 250 mm, internal diameter 4.6 mm. Detection: UV at 254 nm with a diode array detector. Mobile phase of 84 % methanol and 16 % water. Retention time ca. 10 min for avermectin B_{1b} and 12 min for avermectin B_{1a}. RSD can be < 0.5 %.

Validation. Method was validated by IR and HPLC-MS. Reference standard: analytical abamectin ([redacted]). Reference solution was prepared in methanol (1 mg/mL), sonicated and filtered over 0.45 µm. A solution of the test compound was made accordingly, [redacted]

Results

Identity. Identity was confirmed by HPLC-MS and FTIR Spectroscopy and comfirmed by retention times, which did not differ by > 0.2 min.

Specificity. No interference of process related by products.

Linearity. Linearity was demonstrated by analysing duplicate weights of the test sample (technical abamectin) at 80, 100 and 120 % of the sample target weight. Correlation coefficients of weighed versus found was > 0.999, RSD < 0.5 %.

Repeatability. Average amount analysed was 85.1 % for avermectin B_{1a} (n = 6, RSD 0.14 %), and 5.86 % for avermectin B_{1b} (n = 6, RSD 0.17 %).

Ruggedness. Analysis results of a second chemist using different instrument and column were 84.8 % for avermectin B_{1a} (n = 7, RSD 0.29%) and 5.77 % for avermectin B_{1b} (n = 7, RSD 0.69). Relative difference to first analysis was 0.2 and 1.5 %.

Solvolysis. Solutions of abamectin reference and technical abamectin were re-injected after 24 hours, concurrent with a fresh standard. Weight change of avermectin B_{1a} and avermectin B_{1a} in the sample was < 1% for the reference and < 2 % for technical abamectin.

Remarks by RMS

Method meets validity criteria.

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	5 November 2007
Materials and Methods	-
Results and discussion	-
Conclusion	[redacted]
Reliability	-
Acceptability	-
Remarks	-
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion. Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

4.2 (a) Analytical methods for the determination of residues in soil

98/8 Doc IIIA section No.	**4.2 (a)/01**	**Analytical methods for the determination of residues in soil**
91/414 Annex Point addressed	**IIA 4.2.2**	**Analytical methods for determination of residues – residues in soil**

Title of the Study	**Abamectin and its metabolites, Validation of a residue analytical method for the determination of residues in soil**	**For official use only**
Dossier Reference:	4.2 (a)/01	
Method Number: Author:	RJ3431B Emburey, S.N.	
Name and address of the testing facility:	Syngenta Jealott's Hill International Research Centre, Bracknell, UK	
Test substance:	Abamectin	
Date of issue:	2003	
Compliance with GLP:	Yes	
Reliability indicator	1	

Reference/notifier	:	Emburey, S.N. (2003)	GLP statement	:	yes (validation study)
Type of study	:	analytical method soil, validation	Guideline	:	not applicable
Year of execution	:	2003	Acceptability	:	acceptable
Test substance	:	avermectin B_{1a}, batch [redacted], purity [redacted] avermectin B_{1b} (NOA 421704), [redacted], purity [redacted] [8,9-Z]-avermectin B_{1a} (NOA 427011), batch [redacted] purity [redacted] 8a-oxo-avermectin B_{1a} (NOA 448111), batch [redacted] purity [redacted] 8a-hydroxy-avermectin B_{1a} (NOA 448112), batch [redacted] purity [redacted] 4,8a-dihydroxy-avermectin B_{1a} (NOA 457464), batch [redacted] purity [redacted] 4-hydroxy-8a-oxo-avermectin B_{1a} (NOA 457465), batch [redacted] purity [redacted]			

Substrate	Analyte	LOQ [µg/kg]	Recovery fortification level [µg/kg]	Recoveries: range (mean) [%]	Repeatability RSD (n) [%]	Linearity of response (r^2)
sandy loam	avermectin B_{1a}	0.5	0.5	89 – 113 (98)	9 (5)	0.9993
			5	94 – 99 (95)	2 (5)	
	avermectin B_{1b} (NOA 421704)	0.5	0.5	91 – 102 (99)	5 (5)	1
			5	96 – 103 (101)	3 (5)	
	[8,9-Z]-avermectin B_{1a} (NOA 427011)	0.5	0.5	85 – 98 (93)	7 (5)	0.9971
			5	93 – 99 (97)	3 (5)	
	8a-oxo-avermectin B_{1a} (NOA 448111)	0.5	0.5	83 – 97 (91)	6 (5)	0.9997
			5	86 – 93 (90)	3 (5)	
	8a-hydroxy-avermectin B_{1a} (NOA 448112)	0.5	0.5	95 – 108 (101)	5 (5)	0.9998
			5	94 – 96 (96)	2 (5)	
	4,8a-dihydroxy-avermectin B_{1a} (NOA 457464)	0.5	0.5	65 – 93 (82)	13 (5)	0.9999
			5	88 – 91 (90)	2 (5)	
	4-hydroxy-8a-oxo-avermectin B_{1a} (NOA 457465)	0.5	0.5	91 – 102 (95)	5 (5)	0.9998
			5	88 – 94 (92)	3 (5)	
silty clay loam	avermectin B_{1a}	0.5	0.5	75 – 87 (83)	7 (5)	0.9998
			5	72 – 89 (82)	8 (5)	
	avermectin B_{1b} (NOA 421704)	0.5	0.5	77 – 88 (82)	5 (5)	0.9999
			5	78 – 85 (81)	3 (5)	
	[8,9-Z]-avermectin B_{1a} (NOA 427011)	0.5	0.5	75 – 81 (78)	3 (5)	0.9999
			5	69 – 86 (79)	8 (5)	
	8a-oxo-avermectin B_{1a} (NOA 448111)	0.5	0.5	71 – 75 (73)	2 (5)	1
			5	67 – 82 (76)	8 (5)	
	8a-hydroxy-avermectin B_{1a} (NOA 448112)	0.5	0.5	71 – 85 (78)	7 (5)	1
			5	74 – 90 (80)	8 (5)	
	4,8a-dihydroxy-avermectin B_{1a} (NOA 457464)	0.5	0.5	75 – 98 (82)	11 (5)	0.9999
			5	49 – 82 (70)	19 (5)	
	4-hydroxy-8a-oxo-avermectin B_{1a} (NOA 457465)	0.5	0.5	75 – 83 (78)	4 (5)	0.9999
			5	72 – 83 (80)	6 (5)	

Description

Method validation. Soil (sandy loam from Pappelacker and silty clay loam from Scheueracker) was applied with a stock of mixed test substances in acetonitrile/water (50:50). Fortification levels 0.5 and 5 µg/kg with five replicates each, two control replicates.

Analysis method. RAM 412/01. Soil samples (10 g) are extracted three times by shaking with 100 mL acetonitrile/water (70:30, v/v) for 30 min, extracts combined after centrifugation, made up to 200 mL volume, and centrifuged at 3500 rpm for 5 min. to remove fine particulate material. A 40 mL aliquot of extract is reduced to 10 mL by rotary evaporation, 3.3 mL acetonitrile and 2 drops of NH_4OH are added. A Waters Oasis HLB SPE cartridge (Hydrophylic-Lipophylic Balanced; N-vinylpirrolidone and divinylbenzene) is eluted with dichloromethane, methanol and acetonitrile/water (25:75, v/v). The sample is brought on the column, column is dried, washed with hexane and eluted with dichloromethane. Eluate is dried, re-dissolved in acetonitrile/water (1:1, v/v) with ultrasonication. Final determination by LC-MS/MS. Q1 and Q3-masses are given in the table below.

Table: Q1 and Q3-masses for MS-identification of avermectin B_{1a} and related compounds.

Compound	Code	Q1	Q3
avermectin B_{1a}	NOA 422601	890.6	567.1
avermectin B_{1b}	NOA 421704	876.5	553.1
[8,9-Z]-avermectin B_{1a}	NOA 427011	890.6	567.1
8a-oxo-avermectin B_{1a}	NOA 448111	904.5	599.2
8a-hydroxy-avermectin B_{1a}	NOA 448112	906.5	565.1
4,8a-dihydroxy-avermectin B_{1a}	NOA 457464	922.5	581.1
4-hydroxy-8a-oxo-avermectin B_{1a}	NOA 457465	920.5	709.2

Samples re-analysed after 6 days of storage at 5 °C. Matrix effects determined by comparison of fortified control extracts with standard.

Results

LOQ 0.5 µg/kg (lowest fortification level with adequate recovery). LOD, defined as 4 x background, 0.01 and 0.08 µg/kg. Linearity demonstrated. Recovery of fortified samples as reported in header. Matrix effects between 12.6 % suppression and 10.1 % enhancement of signal. Storage stability for 6 days at 5 °C demonstrated except for NOA 448112, NOA 457464 and NOA 457465, where recovery was outside 70 – 110 % and/or RSD was > 20 %.

Remarks by RMS

Lower recovery and repeatability in silty clay loam. The method is not validated for the compound [8,9-Z]-avermectin B1b from the residue definition. This is acceptable because it can be expected that this compound will behave the same as the B1a variant. Additional all the other compounds show a good performance with low LOQ. Method meets validity criteria.

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	16 June 2008
Materials and Methods	-
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	-
Acceptability	[redacted]

Remarks	-
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion. Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

4.2 (b) Analytical methods for the determination of residues in air

98/8 Doc IIIA section No.	**4.2 (b)/01**	**Analytical methods for the determination of residues in air**
91/414 Annex Point addressed	**IIA 4.2.4**	**Analytical methods for determination of residues – residues in air**

Title of the Study	**Determination of avermectin B1a (NOA 422601) and avermectin B1b (NOA 421704) by high performance liquid chromatography**	**For official use only**
Dossier Reference:	4.2 (b)/01	
Method Number: Author:	REM 198.01 Tribolet, R.	
Name and address of the testing facility:	Novartis Crop Protection AG, CH-4002 Basel, Switzerland	
Test substance:	Abamectin	
Date of issue:	2000a	
Compliance with GLP:	No, but complies with sound scientific principles	
Reliability indicator	1	

For the study summary see Document IIIA reference point 4.2 (b)/02.

98/8 Doc IIIA section No.	**4.2 (b)/02**	**Analytical methods for the determination of residues in air**
91/414 Annex Point addressed	**IIA 4.2.4**	**Analytical methods for determination of residues – residues in air**

Title of the Study:	**Validation of method REM 198.01 by analyses of fortified air sampling tubes for avermectin B1a, and avermectin B1b and evaluation of recoveries**	**For official use only**
Dossier Reference:	4.2 (b)/02	
Method number: Author:	105/99 Tribolet, R.	
Name and address of testing facility:	Novartis Crop Protection AG, CH-4002 Basel, Switzerland	
Test substance:	Abamectin	
Date of issue:	2000b	
Compliance with GLP:	Yes	
Reliability indicator	1	

Reference/notifier	:	Tribolet, R. (2000a, b)	GLP statement	:	yes (validation study)
Type of study	:	analytical method air, validation	Guideline	:	not applicable
Year of execution	:	1999-2000	Acceptability	:	acceptable
Test substance	:	avermectin B_{1a}, batch [redacted], purity [redacted] avermectin B_{1b}, batch [redacted], purity [redacted]			

Substrate	Analyte	LOQ	Recovery fortification level	Recoveries: range (mean)	Repeatability RSD (n)	Linearity of response
		[µg/m^3]	[µg/m^3]	[%]	[%]	(SD %)
air	avermectin B_{1a}	0.1	0.1	99 - 109 (104)	5 (5)	4.7
			10	84 - 88 (87)	2 (5)	
air	avermectin B_{1b}	0.1	0.1	73 - 77 (75)	3 (5)	4.7
			10	85 - 89 (88)	2 (5)	

Description

Method validation. Air sampling tubes with subsequent layers of glass fiber filter, XAD-2 sorbent, polyurethane foam, XAD-2 sorbent and polyurethane foam, were connected to air sampler. Glass filters were applied with 10 µL solutions of avermectin B_{1a} and B_{1b} in methanol. Solution concentrations 7.2 and 720 µg/mL, corresponding fortification levels 0.1 and 10 µg/m^3 at 6 hours sampling at 2 L/min (total air volume 720 L). Sampling tubes were kept at 36 - 37 °C, 82 % RH. Six additional tubes spiked at 1.44 µg (corresponding to 2 µg/m^3 at 720 L), air-sucked for 5 min. and then stored at -20 °C for 2 months.

Analysis method. REM 198.01. Glass fiber filter and first XAD-layer are put into flask, polyurethane foam and second XAD-layer into another. Layers are extracted twice with methanol for 5 min. in an ultrasonic bath, methanol extracts are combined. Samples are evaporated to dryness and re-dissolved in acetonitrile/water (60/40, v/v) and filtered over 0.45 µm. Final determination by HPLC-UV (243 nm). Columns: Discovery RP Amide C-16, particle size 5 µm, and Inertsil ODS II, particle size 5 µm. Suggested confirmatory technique: MK 936/23 (HPLC Fluorescence determination for avermectin B1 and its 8,9-isomer in cucumbers, Merck Research Laboratories, USA 25 October 1989.

Results

LOQ 0.1 µg/m^3 (lowest fortification level with adequate recovery). The required LOQ according to sanco/825/00 is 3.6 µg/m3, based on an AOEL of 0.0012 mg/kg bw/day.

Linearity demonstrated, standard deviation of straight response function 4.7 %. Recovery of fortified samples as reported in header. No break through to second XAD-layer. Storage stability demonstrated, recovery 102 - 103 % of nominal after correction for procedural recovery.

Remarks by RMS

No remarks. Method meets validity criteria.

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	16 June 2008
Materials and Methods	-
Results and discussion	[redacted]

	[redacted]
	[redacted]
	[redacted]
Conclusion	[redacted]
Reliability	-
Acceptability	[redacted]
Remarks	
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion. Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

4.2 (c) Analytical methods for the determination of residues in water

98/8 Doc IIIA section No.	**4.2 (c)/ 01**	**Analytical methods for the determination of residues in water**
91/414 Annex Point addressed	**IIA 4.2.3**	**Analytical methods for determination of residues – residues in water**

Title of the Study	**Residue analytical method for the determination of residues of avermectins NOA 422601, NOA 421704, NOA 427011, NOA 426289 and NOA 445495 in environmental water samples. Final determination by LC-MS/MS**	**For official use only**
Dossier Reference:	4.2 (c)/01	
Method Number: Author:	RAM 413/01 Hargreaves, S.L.	
Name and address of the testing facility:	Syngenta Jealott's Hill International Research Centre, Bracknell, UK	
Test substance:	Abamectin	
Date of issue:	2003a	
Compliance with GLP:	No, but complies with sound scientific principles	
Reliability indicator	1	

For the study summary see Document IIIA reference point 4.2 (c)/02.

98/8 Doc IIIA section No.	**4.2 (c)/ 02**	**Analytical methods for the determination of residues in water**
91/414 Annex Point addressed	**IIA 4.2.3**	**Analytical methods for determination of residues – residues in water**

Title of the Study	**Abamectin: Validation of a residue analytical method for the determination of residues of NOA 422601, NOA 421704, NOA 427011, NOA 426289 and NOA 445495 in water**	**For official use only**
Dossier Reference:	4.2 (c)/02	
Method Number: Author:	RJ3389B Hargreaves, S.L.	
Name and address of the testing facility:	Syngenta Jealott's Hill International Research Centre, Bracknell, UK	
Test substance:	Abamectin	
Date of issue:	2003b	
Compliance with GLP:	Yes	
Reliability indicator	1	

Reference/notifier	:	Hargreaves, S.L. (2003a) Hargreaves, S.L. (2003b)	GLP statement	:	yes (validation study)
Type of study	:	analytical method water, validation	Guideline	:	not applicable
Year of execution	:	2003	Acceptability	:	acceptable
Test substance	:	avermectin B_{1a}, batch [redacted], purity [redacted] avermectin B_{1b} (NOA 421704), batch [redacted] purity [redacted] [8,9-Z]-avermectin B_{1a} (NOA 427011), batch [redacted] purity [redacted] 4"-oxo-avermectin B_{1a} (NOA 426289), [redacted], purity [redacted] 3"-demethyl-avermectin B_{1a} (NOA 445495), batch [redacted], purity [redacted]			

Substrate	Analyte	LOQ	Recovery fortification level	Recoveries: range (mean)	Repeatability RSD (n)	Linearity of response
		[µg/L]	[µg/L]	[%]	[%]	(r^2)
river water	avermectin B_{1a}	0.05	0.05	89 - 91 (92)	4 (5)	0.9998
			0.5	90 - 100 (95)	4 (5)	
	avermectin B_{1b} (NOA 421704)	0.05	0.05	86 - 95 (91)	4 (5)	0.9995
			0.5	96 - 101 (97)	2 (5)	
	[8,9-Z]-avermectin B_{1a} (NOA 427011)	0.05	0.05	85 - 100 (92)	6 (5)	0.9998
			0.5	92 - 100 (96)	4 (5)	
	4"-oxo-avermectin B_{1a} (NOA 426289)	0.05	0.05	68 - 86 (77)	11 (5)	0.9996
			0.5	70 - 84 (78)	7 (5)	
	3"-demethyl-avermectin B_{1a} (NOA 445495)	0.05	0.05	73 - 85 (77)	6 (5)	0.9999
			0.5	76 - 95 (84)	10 (5)	
ground water	avermectin B_{1a}	0.05	0.05	84 - 93 (89)	5 (5)	0.9995
			0.5	92 - 95 (94)	1 (5)	
	avermectin B_{1b} (NOA 421704)	0.05	0.05	87 - 92 (90)	3 (5)	0.9995
			0.5	91 - 96 (93)	2 (5)	
	[8,9-Z]-avermectin B_{1a} (NOA 427011)	0.05	0.05	82 - 99 (90)	8 (5)	0.9996
			0.5	88 - 93 (90)	2 (5)	
	4"-oxo-avermectin B_{1a} (NOA 426289)	0.05	0.05	61 - 80 (72)	10 (5)	0.9995
			0.5	73 - 84 (77)	6 (5)	
	3"-demethyl-avermectin B_{1a} (NOA 445495)	0.05	0.05	76 - 83 (79)	3 (5)	0.9998
			0.5	67 - 88 (80)	10 (5)	
drinking water	avermectin B_{1a}	0.05	0.05	83 - 95 (89)	5 (5)	0.9998
			0.5	92 - 100 (95)	3 (5)	
	avermectin B_{1b} (NOA 421704)	0.05	0.05	91 - 102 (94)	5 (5)	0.9999
			0.5	96 - 100 (98)	2 (5)	
	[8,9-Z]-avermectin B_{1a} (NOA 427011)	0.05	0.05	83 - 91 (86)	4 (5)	0.9998
			0.5	92 - 96 (93)	2 (5)	
	4"-oxo-avermectin B_{1a} (NOA 426289)	0.05	0.05	76 - 94 (84)	9 (5)	0.9999
			0.5	83 - 99 (87)	9 (5)	
	3"-demethyl-avermectin B_{1a} (NOA 445495)	0.05	0.05	73 - 85 (77)	6 (5)	0.9994
			0.5	72 - 91 (82)	10 (5)	

Description

Method validation. Three water types were applied with a stock of mixed test substances in acetonitrile. Fortification level 0.05 and 0.5 µg/L with five replicates each, two control replicates. Water characteristics are given in the table below.

Table: Characteristics of water used in validation study.

Water type	Source	pH	Silt	DOC	Total hardness
			[% w/w]	[mg/L]	[mg $CaCO_3$/L]
River water	River Thames, Wargrave, UK	7.60	< 1	< 2.0	291
Ground water	Sheeplands Farm, Wargrave, UK	7.47	< 1	< 2.0	565
Drinking water	Jealott's Hill Research Station	7.56	N/A	< 2.0	327

Analysis method. RAM 413/01. Water samples are diluted with acetonitrile, final acetonitrile content 25 % v/v. An Oasis® HLB SPE cartridge is eluted with methanol and ultrapure water. Sample is brought on the column, column eluted with acetonitrile. Eluate is diluted to 2.5 mL with ultrapure water. Samples are transferred to silanised vials for final determination by LC-MS/MS. Q1 and Q3-masses are given in the table below.

Table: Q1 and Q3-masses for MS-identification of avermectin B_{1a} and related compounds.

Compound	Code	Q1	Q3
avermectin B_{1a}	NOA 422601	876.5	553.1
avermectin B_{1b}	NOA 421704	890.6	567.1
[8,9-Z]-avermectin B_{1a}	NOA 427011	876.5	553.1
4"-oxo-avermectin B_{1a}	NOA 426289	888.6	565.1
3"-demethyl-avermectin B_{1a}	NOA 445495	876.0	567.2

The ammonium adducts of molecular ions generated in the ion source are selected (m/z 890.6 for avermectin B_{1a} and [8,9-Z]-avermectin B_{1a}, m/z 876.5 for avermectin B_{1b}, m/z 888.6 for 4"-oxo-avermectin B_{1a}, and m/z 876.0 for 3"-demethyl-avermectin B_{1a}) and subjected to further fragmentation by collisional activation. The most selective ion for each analyte (m/z 567.1 for avermectin B_{1a} and [8,9-Z]-avermectin B_{1a}, m/z 553.1 for avermectin B_{1b}, m/z 565.1 for 4"-oxo-avermectin B_{1a}, and m/z 567.2 for 3"-demethyl-avermectin B_{1a}) in the resulting daughter spectra is monitored and used for quantitative analysis. Matrix effects determined by comparison of fortified control extracts with standard.

Results

LOQ 0.05 µg/L (lowest fortification level with adequate recovery). LOD, defined as 4 x background, ≤ 0.01 µg/L. Linearity demonstrated. Recovery of fortified samples as reported in header. Matrix effects between < 1 % suppression and 23 % enhancement of signal for avermectin B_{1a}, avermectin B_{1b}, [8,9-Z]-avermectin B_{1a}, 3"-demethyl-avermectin B_{1a}, and for 4"-oxo-avermectin B_{1a} in drinking water. Enhancement of signal for 4"-oxo-avermectin B_{1a} in river and groundwater 96 and 154 %.

Remarks by RMS

No remarks. Method meets validity criteria.

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	16 June 2008
Materials and Methods	-
Results and discussion	[redacted]
	[redacted]
Conclusion	[redacted]
Reliability	-

Acceptability	[redacted]
Remarks	-
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion. Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

4.2 (d) Analytical methods for the determination of residues in animal and human body fluids and tissues

98/8 Doc IIIA section No.	**4.2 (d)/01**	**Analytical methods for the determination of residues in animal and human body fluids and tissues**
91/414 Annex Point addressed	**II 4.2.1**	**Analytical methods for determination of residues – residues in plants/foodstuffs/feedingstuffs**

Title of the Study	**Determination of avermectin B1a, avermectin B1a 8,9-Z isomer and avermectin B1b by LC-LC-MS/MS in plant substrates and animal tissues**	**For official use only**
Dossier Reference:	4.2 (d)/01	
Method Number: Author:	REM 198.02 [redacted]	
Name and address of the testing facility:	[redacted]	
Test substance:	Abamectin	
Date of issue:	2002a	
Compliance with GLP:	No, but complies with sound scientific principles	
Reliability indicator	1	

For the study summary see Document IIIA reference point 4.2 (d)/03.

98/8 Doc IIIA section No.	**4.2 (d)/02**	**Analytical methods for the determination of residues in animal and human body fluids and tissues**
91/414 Annex Point addressed	**II 4.2.1**	**Analytical methods for determination of residues – residues in plants/foodstuffs/feedingstuffs**

Title of the Study	**Validation of method REM 198.02, Validation by analysis of specimens of tomatoes, oranges, cotton seed, hops, milk, eggs and blood fortified with abamectin (MK 936), and determination of recoveries**	**For official use only**
Dossier Reference:	4.2 (d)/02	
Method Number: Author:	REM 198.02 [redacted]	
Name and address of the testing facility:	[redacted]	
Test substance:	Abamectin	
Date of issue:	2002b	
Compliance with GLP:	Yes	
Reliability indicator	1	

For the study summary see Document IIIA reference point 4.2 (d)/03.

98/8 Doc IIIA section No.	**4.2 (d)/03**	**Analytical methods for the determination of residues in animal and human body fluids and tissues**
91/414 Annex Point addressed	**II 4.2.1**	**Analytical methods for determination of residues – residues in plants/foodstuffs/feedingstuffs**

Title of the Study	**Inter-laboratory validation of residue method REM 198.02 in tomatoes, hops, meat and milk**	**For official use only**
Dossier Reference:	4.2 (d)/03	
Method Number: Author:	REM 198.02 [redacted]	
Name and address of the testing facility:	[redacted]	
Test substance:	Abamectin	
Date of issue:	2002	
Compliance with GLP:	Yes	
Reliability indicator	1	

[Method REM 198.02 is identical to method MSD 8920 mod.]

Method REM 198.02 was developed to have a method that allows for individual determination of avermectin B1a, avermectin B1b and the 8,9-Z isomer of avermectin B1a in plant material and foodstuffs of animal origin. It is proposed as enforcement method and is used as analytical method in supervised residue trials on citrus, tomato and lettuce and in a processing study on tomato and tomato products. As enforcement method, it should comply with European guidelines as described in SANCO/825/00 rev.6. As method for residue trials, it should comply with European guidelines as described in SANCO/3029/99 rev. 4. The method and its validation are described by [redacted] in two separate reports. An inter-laboratory validation is reported by [redacted]. In addition, concurrent recoveries from the supervised trials are used for validation.

Since no significant residues are expected to occur in livestock feed, it is deemed unnecessary to propose a residue definition for animal products or propose MRLs for animal products. Therefore no analytical method for animal products is required. Method REM 198.02 was also validated for three animal commodities. Results for these animal commodities are taken up in the summary below but are not assessed.

Reference/notifier	:	[redacted]	GLP statement	:	No
Type of study	:	Analytical method in plant and animal foodstuff	Guideline	:	-
Year of execution	:	2002	Acceptability	:	Acceptable
Test substance	:	Avermectin B1a [redacted] avermectin B1b [redacted] and 8,9-Z isomer of avermectin B1a [redacted]			

Reference/notifier	:	[redacted] 2002b	GLP statement	:	Yes
Type of study	:	Analytical method in plant and animal foodstuff	Guideline	:	EC 8064/VI/97 and OPPTS 860.1340 PR notice 96-1
Year of execution	:	2002	Acceptability	:	Acceptable
Test substance	:	Avermectin B1a [redacted] avermectin B1b [redacted] and 8,9-Z isomer of avermectin B1a [redacted]			

Reference/notifier	:	[redacted] 2002	GLP statement	:	Yes
Type of study	:	Analytical method in plant and animal foodstuff	Guideline	:	-
Year of execution	:	2002	Acceptability	:	Acceptable
Test substance	:	Avermectin B1a [redacted] avermectin B1b [redacted] and 8,9-Z isomer of avermectin B1a [redacted]			

Reference/notifier	:	Solé 2004	GLP statement	:	Yes
Type of study	:	Residue study with abamectin (MK936) in or on tomatoes in spain	Guideline	:	-
Year of execution	:	2004	Acceptability	:	Acceptable
Test substance	:	Avermectin B1a [redacted] avermectin B1b [redacted] and 8,9-Z isomer of avermectin B1a [redacted]			

Description of the method: Sample preparation and clean-up vary depending on the type of substrate. Homogenised samples of aqueous substrates (tomatoes, oranges) are extracted by maceration with methanol. After centrifugation the extract is cleaned up on a C8-coated solid phase extraction (SPE) tube. Analytes are eluted with methanol. Homogenised samples of fatty/oily substrates (cotton seed, meat, milk, and eggs) are extracted by maceration with methanol. After filtration the extract is cleaned up on an amino coated SPE, washed by partitioning with n-hexane and cleaned up on a C8-coated SPE tube. Analytes are eluted with methanol. Homogenised samples of hops (fresh and dried cones) are extracted by shaking with water and methanol. After addition of a 5% calcium chloride solution the water/methanol phase is partitioned with n-hexane and the organic phase is cleaned up on an amino-coated SPE tube. Analytes are eluted with a mixture of ethyl acetate/methanol. Avermectin B1a, avermectin B1b and the 8,9-Z isomer of avermectin B1a are quantified in a single run with a two-column switch HPLC system (phenyl and C18 column) and MS/MS detection (positive ion mode, detection at 890.5 and 567.2 for avermectin B1a and its 8,9-Z isomer and at 876.4 and 553.3 for avermectin B1b).

Validation results: The linearity of the detector response was verified for each analyte with 6 concentration levels in the range 0.50-20 µg/L (not stated in mg/kg units) with 2-3 injections per level with correlation coefficient of the weighted regression line above 0.99. The matrix was unstated (probably pure solvent). The method was validated by conducting recovery experiments. Samples of tomato, orange, cotton seed, hops (green and dried), meat, milk and eggs were spiked after homogenisation with avermectin B1a, avermectin B1b and the 8,9-Z

isomer of avermectin B1a at fortification levels of 0.01-0.1 mg/kg for hops and 0.002-0.02 mg/kg for other matrices. Five fortified samples were analysed for each fortification level. Recovery and repeatability results are shown in Table B.5.2.1-1. Validation results for orange at 0.002 mg/kg showed for 1 of 5 samples very high recoveries for all three analytes (157-186%). For meat at 0.002 mg/kg and eggs at 0.02 mg/kg recoveries for 1 of the 5 samples were very low for all three analytes (17-38%). These samples were considered outliers and were removed by the study author without any further explanation. Because the deviating recovery results apply to all three analytes in the same degree, the RMS is inclined to believe an error occurred in spiking the sample and accepts the removal of these results. In 2 control samples per matrix, residue levels were below LOQ. The reported LOQ is 0.002 mg/kg in tomato, orange, cotton seed, meat, milk and eggs and 0.01 mg/kg in hops.

An independent laboratory validation was conducted with tomato, green hops, (beef) meat and milk. The recovery analyses included 5 samples fortified at LOQ and 5 samples at 10xLOQ. The linearity of the detector response was verified with 6 concentration levels in the range 0.5-20 µg/L (not stated in mg/kg units) with an unstated number of injections per level with correlation coefficient of the regression line above 0.99. The matrix was unstated (probably pure solvent). Recovery and repeatability results are shown in Table B.5.2.1-1. In 2 control samples per matrix, residue levels were below LOQ. The reported LOQ is 0.002 mg/kg in tomato, meat, and milk and 0.01 mg/kg in green hops. In [redacted] 2004 additional recovery validation is presented. For tomato processed matrices, lettuce and mandarin, results of concurrent recoveries from the supervised trials are taken for validation and are presented in the table below.

Table: Validation results for method REM 198.02

Substrate	Analyte	reported LOQ [mg/kg]	Recovery fortification level [mg/kg]	Recoveries: range (mean) [%]	Repeatability RSD (n) [%]	Linearity of response (r^2)
Orange (a)	avermectin B1a	0.002	0.002	98-112 (106)	7 (4)*	X
			0.02	89-98 (91)	4 (5)	
	8,9-Z isomer of B1a	0.002	0.002	81-93 (87)	6 (4)*	
			0.02	82-94 (86)	6 (5)	
	avermectin B1b	0.002	0.002	99-106 (102)	3 (4)*	
			0.02	92-100 (96)	3 (5)	
Mandarin (c)	avermectin B1a	0.002	0.002	74-93 (82)	12 (3)	X
			0.02	76-97 (84)	14 (3)	
	8,9-Z isomer of B1a	0.002	0.002	65-94 (78)	19 (3)	
			0.02	69-93 (78)	16 (3)	
	avermectin B1b	0.002	0.002	76-97 (84)	13 (3)	
			0.02	79-99 (87)	12 (3)	
Tomato (a)	avermectin B1a	0.002	0.002	75-86 (80)	5 (5)	X
			0.02	84-86 (85)	1 (5)	
	8,9-Z isomer of B1a	0.002	0.002	77-99 (85)	6 (5)	
			0.02	80-85 (82)	2 (5)	
	avermectin B1b	0.002	0.002	77-90 (85)	7 (5)	
			0.02	89-96 (91)	3 (5)	
Tomato (ILV)	avermectin B1a	0.002	0.002	93-107 (99)	5.3 (5)	X
			0.02	79-84 (82)	2.9 (5)	
	8,9-Z isomer of B1a	0.002	0.002	89-97 (92)	3.7 (5)	
			0.02	80-91 (86)	4.5 (5)	
	avermectin B1b	0.002	0.002	93-98 (96)	2.4 (5)	
			0.02	84-100 (91)	7.5 (5)	
Tomato (e)	avermectin B1a	0.002	0.002	85-91 (87)	3 (5)	unknown
			0.01	95-111 (102)	6 (5)	
			0.02	91-97 (94)	2 (5)	
			0.10	96-113 (103)	7 (5)	
	8,9-Z isomer of B1a	0.002	0.002	88-99 (92)	5 (5)	
			0.01	92-110 (103)	9 (5)	
			0.02	85-94 (91)	4 (5)	
			0.10	93-107 (99)	6 (5)	
	avermectin B1b	0.002	0.002	92-97 (94)	2 (5)	
			0.01	94-104 (100)	4 (5)	
			0.02	88-93 (91)	2 (5)	
			0.10	95-108(102)	5 (5)	
Tomato washing water (b)	avermectin B1a	0.002	0.002	86	- (1)	X
			0.02	83	- (1)	
	8,9-Z isomer of B1a	0.002	0.002	79	- (1)	
			0.02	74	- (1)	
	avermectin B1b	0.002	0.002	78	- (1)	
			0.02	90	- (1	
Wet tomato pomace (b)	avermectin B1a	0.002	0.002	90	- (1)	X
			0.02	99	- (1)	
	8,9-Z isomer of B1a	0.002	0.002	88	- (1)	
			0.02	78	- (1)	
	avermectin B1b	0.002	0.002	79	- (1)	
			0.02	90	- (1	
Tomato raw juice (b)	avermectin B1a	0.002	0.002	107	- (1)	X
			0.02	96	- (1)	
	8,9-Z isomer of B1a	0.002	0.002	102	- (1)	
			0.02	92	- (1)	
	avermectin B1b	0.002	0.002	111	- (1)	
			0.02	101	- (1	
Peeled tomato (b)	avermectin B1a	0.002	0.002	114	- (1)	X
			0.02	99	- (1)	
	8,9-Z isomer of B1a	0.002	0.002	93	- (1)	
			0.02	97	- (1)	
	avermectin B1b	0.002	0.002	97	- (1)	
			0.02	103	- (1	
Tomato preserves (b)	avermectin B1a	0.002	0.002	99	- (1)	X
			0.02	100	- (1)	
	8,9-Z isomer of B1a	0.002	0.002	99	- (1)	
			0.02	98	- (1)	
	avermectin B1b	0.002	0.002	108	- (1)	
			0.02	111	- (1)	

Substrate	Analyte	reported LOQ [mg/kg]	Recovery fortification level [mg/kg]	Recoveries: range (mean) [%]	Repeatability RSD (n) [%]	Linearity of response (r^2)
Raw tomato puree (b)	avermectin B1a	0.002	0.002	100-101 (100)	- (2)	X
			0.02	86-90 (88)	- (2)	
	8,9-Z isomer of B1a	0.002	0.002	87-89 (88)	- (2)	
			0.02	87-87 (87)	- (2)	
	avermectin B1b	0.002	0.002	81-90 (86)	- (2)	
			0.02	90-90 (90)	- (2)	
Lettuce (d)	avermectin B1a	0.002	0.002	76-96 (87)	8.3 (8)	X
			0.02	85-108 (94)	7.2 (8)	
			0.20	92	- (1)	
	8,9-Z isomer of B1a	0.002	0.002	70-121 (88)	17 (8)	
			0.02	73-97 (86)	8.1 (8)	
			0.20	90	- (1)	
	avermectin B1b	0.002	0.002	75-93 (86)	8.2 (8)	
			0.02	79-110 (91)	12 (8)	
				95	- (1)	
Cotton seed (a)	avermectin B1a	0.002	0.002	88-96 (92)	3 (5)	X
			0.02	90-97 (94)	3 (5)	
	8,9-Z isomer of B1a	0.002	0.002	84-93 (90)	5 (5)	
			0.02	87-96 (92)	4 (5)	
	avermectin B1b	0.002	0.002	94-110 (101)	7 (5)	
			0.02	97-102 (100)	2 (5)	
Hops (dried) (a)	avermectin B1a	0.01	0.01	53-71 (62)	11 (5)	X
			0.1	57-62 (60)	4 (5)	
	8,9-Z isomer of B1a	0.01	0.01	52-70 (59)	13 (5)	
			0.1	54-62 (57)	6 (5)	
	avermectin B1b	0.01	0.01	61-80 (70)	12 (5)	
			0.1	60-66 (64)	4 (5)	
Hops (green) (a)	avermectin B1a	0.01	0.01	99-106 (103)	3 (5)	X
			0.1	95-100 (97)	2 (5)	
	8,9-Z isomer of B1a	0.01	0.01	91-97 (95)	3 (5)	
			0.1	88-92 (89)	2 (5)	
	avermectin B1b	0.01	0.01	100-110 (107)	4 (5)	
			0.1	96-98 (97)	1 (5)	
Hops (green) (ILV)	avermectin B1a	0.01	0.01	70-75 (74)	2.8 (5)	X
			0.1	70-80 (77)	5.0 (5)	
	8,9-Z isomer of B1a	0.01	0.01	70-89 (78)	9.2 (5)	
			0.1	72-78 (76)	3.2 (5)	
	avermectin B1b	0.01	0.01	75-95 (85)	9.0 (5)	
			0.1	73-87 (80)	6.9 (5)	
Meat (a)	avermectin B1a	0.002	0.002	84-112 (97)	12 (4)*	X
			0.02	93-119 (101)	11 (5)	
	8,9-Z isomer of B1a	0.002	0.002	77-111 (95)	16 (4)*	
			0.02	90-115 (100)	11 (5)	
	avermectin B1b	0.002	0.002	100-124 (107)	11 (4)*	
			0.02	98-116 (105)	7 (5)	
Meat (ILV)	avermectin B1a	0.002	0.002	70-93 (80)	13 (5)	X
			0.02	73-87 (78)	6.8 (5)	
	8,9-Z isomer of B1a	0.002	0.002	73-92 (83)	9.1 (5)	
			0.02	74-80 (77)	3.0 (5)	
	avermectin B1b	0.002	0.002	72-92 (78)	11 (5)	
			0.02	70-89 (81)	8.3 (5)	
Milk (a)	avermectin B1a	0.002	0.002	79-94 (87)	6 (5)	X
			0.02	92-98 (95)	3 (5)	
	8,9-Z isomer of B1a	0.002	0.002	79-96 (89)	7 (5)	
			0.02	85-93 (89)	4 (5)	
	avermectin B1b	0.002	0.002	82-104 (95)	9 (5)	
			0.02	99-102 (100)	1 (5)	
Milk (ILV)	avermectin B1a	0.002	0.002	101-110 (104)	3.3 (5)	X
			0.02	77-82 (80)	2.5 (5)	
	8,9-Z isomer of B1a	0.002	0.002	78-102 (91)	12 (5)	
			0.02	77-84 (82)	4.6 (5)	
	avermectin B1b	0.002	0.002	76-88 (83)	6.1 (5)	
			0.02	83-92 (87)	4.3 (5)	
Eggs (a)	avermectin B1a	0.002	0.002	86-103 (93)	7 (5)	X
			0.02	71-89 (82)	10 (4)*	
	8,9-Z isomer of B1a	0.002	0.002	79-97 (87)	10 (5)	
			0.02	67-77 (73)	7 (4)*	
	avermectin B1b	0.002	0.002	98-111 (104)	5 (5)	
			0.02	82-104 (96)	10 (4)*	

(a) = [redacted] 2002b; (b) concurrent recovery from [redacted] 2003n; (c) concurrent recoveries from [redacted] 2001g-i and [redacted] 2003a; (d) concurrent recoveries from [redacted] 2000a-c, [redacted] 2001a-c-e-f, and [redacted] 2001a-b; (e) concurrent recovery from [redacted] 2004; (ILV) = independent laboratory validation by [redacted] 2002; X = linearity in solvent >0.99 but not examined per matrix; * One of five samples was considered to be an outlier and was removed by the study author without any further explanation. Because the deviating recovery results apply to all three analytes in the same degree, the RMS is inclined to believe an error occurred in spiking the sample and accepts the removal of these results.

Assessment (for plant commodities): It is important to keep in mind that method REM 198.02 is not only proposed as enforcement method but is also used as analytical method for residue trials, since there are different criteria for these two kinds of methods. First, the similar criteria are discussed collectively and subsequently the specific criteria separately.

The method is fully described. It is validated for all components in the residue definition separately. Repeatability falls inside the required range (<20%) for all tested commodities. Recovery results are insufficient for dried hops because mean values fall outside the required range of 70-110%. Mean recoveries for tomato (products), orange, cotton seed, and green hops fall inside the required range of 70-110%, except for peeled tomato. The number of 1-2 recoveries is not sufficient for tomato products. The number of 4 recoveries is not sufficient for orange because 1 sample was removed as outlier. However, given the sound results in the original study and ILV, in this case the recovery is accepted by the RMS and considered to be sufficient for all tested matrices, except dried hops and tomato products. Tomato is representative for the crop group of commodities with high water content (water). Orange is representative for the crop group of commodities with high water and high acid content (acid). Cotton seed is representative for the crop group of fatty dry commodities (fat). Green hops is a special commodity and does not belong to a certain crop group.

There is no separate confirmatory technique, but this is not required for a specific technique such as HPLC-MS/MS. The measurement range includes LOQ to 10xLOQ. It also includes the proposed provisional MRL for citrus (0.01 mg/kg) and the proposed provisional MRL for tomato (0.05 mg/kg). The calibration model contains a sufficient number of concentration levels with correlation coefficient above the required 0.99 for each analyte in solvent. Matrix effects were not verified. However, because mean recovery results are within required limits, there is no reason to investigate possible matrix effects and no further information is required. Controls are reported to contain residues below the respective LOQ, but it is not reported whether residues are below the required limit of 30% LOQ. Examination of the raw data shows no distinct peaks in control samples. The peak areas for control samples are indeed below 30% of the peak areas for samples fortified at LOQ. So matrix interference is considered to be sufficiently reported.

Enforcement method. The following assessment factors are specifically relevant for an enforcement method. The method is conducted with HPLC-MS/MS, which is a commonly available technique. The method should preferably be included in a multi-residue method. However, it is argued by the notifier that this was not examined because HPLC is only recently

considered as commonly available and GC-analysis is impossible due to the high molecular weight of the analytes.

Validation is required for those crop groups for which an admission is requested, in this case commodities with high water content (tomato, lettuce) and commodities with high water and high acid content (citrus). The latter crop group is covered by the recovery of orange, and the first by the recovery of tomato. An independent laboratory validation was conducted in 2 plant groups with sufficient mean recoveries and precisions.

Method for residue trials. The following assessment factors are specifically relevant for method for residue and processing trials. Validation is required for all sample matrices that are analysed, in this case tomato, tomato products, lettuce, orange and mandarin. The mean recovery and repeatability fall within the required limits for all these matrices, except peeled tomato. The measurement range is sufficient for the levels measured in the residue trials. The number of recoveries is sufficient for tomato, lettuce and orange. For mandarin, only reduced validation data are sufficient because it falls in the same crop group as orange and these are obtained from the concurrent recoveries. For tomato processed products, the number of concurrent recoveries is too low and validation for tomato products is insufficient. Reduced validation data would suffice. Because the 'balance' of total and fractions was not clear, the residue study was not considered acceptable. However the residue levels are <0.05 mg/kg so additional information is not required.

Conclusion: With regard to the use as enforcement method: method 198.02 is sufficiently validated and has a LOQ of 0.002 mg/kg for the crop group commodities with high water and high acid content and fatty dry commodities and 0.01 mg/kg for special commodity green hops.

With regard to the use as method for residue trials, method 198.02 is sufficiently validated for tomato, lettuce, mandarin and orange with a LOQ of 0.002 mg/kg. No enforcement method in animal products is required. However, because abamectin is classified as very toxic (T+), methods are required in tissues and (whole) blood. Method 198.02 is sufficiently validated and has a LOQ of 0.002 mg/kg for meat. A method for blood is still required.

Excerpt from "Comments of Syngenta on the draft assessment report on abamectin (14.07.06)"

The RMS stated that an analytical method for analysis of abamectin residues in whole blood was required because abamectin is classified as 'very toxic'.

Syngenta included an analytical method (REM 198.02) in the dossier submitted to the Commission in support of inclusion of abamectin in Annex I of Council Directive 91/414/EEC (M-II, Section 2-4.2.1). This method was developed to analyse residues of avermectin B1a, avermectin B1b and avermectin B1a 8,9-Z isomer in plant and animal matrices and in whole blood.

Syngenta therefore believes that Method REM 198.02 for the determination of abamectin residues in

blood fulfils the current EU requirements for recoveries and precision (repeatability and robustness).
[See Supplement 1 to this table, Part 5, for full method details].

Supplement 1 to this table, Part 5:
Method REM 198.02 was included in the dossier submitted to the Commission in support of the inclusion of abamectin in Annex I of Council Directive 91/414/EEC (M-II, Section 2-4.2.1): This method was developed to analyse residues of avermectin B1a, avermectin B1b and avermectin B1a 8,9-Z isomer in plant and animal matrices and in whole blood.

Report:	[redacted] (2002). Determination of avermectin B1a, avermectin B1a 8,9-Z isomer and avermectin B1b by LC-LC-MS/MS in plant substrates and animal tissues. Report No. REM 198.02, [redacted] Syngenta File No. MK936/0832).
Guidelines:	None stated
Deviations:	N/A
GLP:	No

The following study (which included a validation of this method in whole blood) was also included in the dossier submitted to the Commission in support of the inclusion of abamectin in Annex I of Council Directive 91/414/EEC (M-II, Section 2-4.2.1):

Report:	[redacted] (2002). Validation of method REM 198.02, Validation by analysis of specimens of tomatoes, oranges, cotton seed, hops, milk, eggs and blood fortified with abamectin (MK936) and determination of recoveries. Report No. 02-S101, [redacted] Syngenta File No. MK936/0833).
Guidelines:	Guidance Document for residue analytical methods 8064/VI/97 of the European Commission Residue Chemistry Test Guidelines OPPTS860.1340, PR Notice 96-1
Deviations:	None
GLP:	Fully GLP compliant study

Materials and methods:

Method REM 198.02 was validated by fortification of untreated specimens of tomatoes, oranges. cotton seed, hops, milk, eggs and whole blood with avermectin B1a, avermectin B1a 8,9-Z isomer and avermectin B1b.
Control samples were analysed in duplicate and fortified samples were analysed in quintuplet at the limit of quantification (LOQ 0.002 mg/kg) and ten times the LOQ.

Findings:

Only the findings for whole blood are summarised in this section.

Acceptable mean recoveries in the range of 70% to 110% with a relative standard deviation (RSD) of ≤ 20% were found at both fortification levels. There were no residues of abamectin at or above 30% of the LOQ of the analytical method in the unfortified control samples.
The mean procedural recovery values and relative standard deviations (RSD) of the analytes in a whole blood matrix were as follows:

Table: Mean procedural recoveries and RSD for whole blood using REM 198.02

Fortification (mg/kg)	Description	Avermectin B1a (NOA422601)	Avermectin B1a 8,9-Z isomer (NOA427011)	Avermectin B1b (NOA421704)
0.002	Mean recovery (%)	95	94	106
	Relative standard deviation (RSD %)	7	10	10

0.020	Mean recovery (%)	91	84	104
	Relative standard deviation (RSD %)	8	7	9

Specificity: Specificity was established and no interference was observed. The HPLC method is able to separate avermectin B1a, avermectin B1b and the 8,9-Z isomer of B1a.

Linearity: Linearity of detector response for the three analytes was established by injecting standards at levels of 0.005. 0.01, 0.02, 0.05, 0.1 and 0.2 mg/kg.

Repeatability: overall relative standard deviations were as follows

s_{rel} = 8% for avermectin B1a
s_{rel} = 10% for avermectin B1a 8,9-Z isomer
s_{rel} = 9% for avermectin B1b

Accuracy: The accuracy of the method was established based on the findings for specificity and linearity.

Precision: The precision of the method was established based on the findings for repeatability and robustness of the method

Conclusion:

Method REM 198.02 for the determination of abamectin residues in blood fulfils the current EU requirements for recoveries and precision (repeatability and robustness) as stated in Annex VI to Council Directive 91/414/EEC (97/57/EC) and Council Directive 96/46/EC.

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	5 November 2007
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	-
Acceptability	[redacted]
Remarks	-
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion. Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

4.2 (e) Analytical methods for the determination of residues in food and feedstuffs

98/8 Section A4.2(e)	Analytical methods for the determination of residues in food and feedstuffs	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ]	Technically not feasible [ ] Scientifically unjustified [ ]	
Limited exposure [ ]	Other justification [X]	
Detailed justification:	[redacted]	
Undertaking of intended data submission [ ]	[redacted]	

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	5 November 2007
Materials and Methods	-
Results and discussion	[redacted]
Conclusion	-
Reliability	-
Acceptability	[redacted]
Remarks	-
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion. Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Abamectin

Document IIIA

Section 5 : Effectiveness Against Target Organisms And Intended Uses

	For official use only
5.1 Function Abamectin is an insecticide.	
5.2 Organism(s) to be controlled and products, organisms or objects to be protected	
5.2.1 Organism(s) to be controlled The efficacy data for abamectin are summarized in IIIB. **Conclusion:** Abamectin is effective against ants and roaches.	X
5.2.2 Products, objects or organisms to be protected Abamectin based formulations are designed to protect industrial buildings, homes and hospitals.	
5.3 Effects on target organisms and likely concentration at which the active substance will be used	
5.3.1 Effects on target organisms Abamectin is active against ants and roaches.	X
5.3.2 Likely concentrations at which the active substance will be used For Product type 18, Abamectin will be manufactured as a concentrate that is diluted to 0.05% for industrial uses and 0.05 % for both professionals and non-professionals.	
5.4 Mode of action (including time delay)	
5.4.1 Mode of action Abamectin exerts its pesticidal effect by interfering with the inhibitory neurotransmitter GABA by altering the gating mechanism and permeation of chloride ions at the neuromuscular junction, causing paralysis.	X
5.4.2 Time delay Although death can be delayed for up to a few hours, the intoxicated insect irreversibly stops feeding.	
5.5 Field of use envisaged Insecticidal use (PT 18).	
5.6 User: industrial, professional, general public (non-professional) Abamectin containing products are used :	

- for industrial premises; the application techniques are as baits
- for indoor (*in situ*) application by professionals. These are baits
- for do-it-yourself *in situ* treatment in and around the house (non-professional); the application techniques are as baits.

5.7 Information on the occurrence or possible occurrence of the development of resistance and appropriate management

5.7.1 Development of resistance

Only a small portion of ant and roach baits are treated with abamectin based products. Hence, the development of resistance to abamectin is unlikely.

The probability of resistance in social insects like ants, roaches is very small because of the long development cycle and the wide range of chemicals with different mode of actions on the market.

5.7.2 Management strategies

In areas where the presence of tolerance strains is confirmed, alternate control methods are recommended (e.g. alternation or combination with other insecticides having a different mode of action).

5.8 Likely tonnage to be placed on the market per year

Approximately [redacted]

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	November 2008
Comments	[redacted]
Conclusion	[redacted]
Reliability	-
Acceptability	[redacted]
Remarks	
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Results and discussion	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	December 2007
Comments	[redacted]

Conclusion	-
Reliability	-
Acceptability	[redacted]
Remarks	-

	COMMENTS FROM ...
Date	*Give date of comments submitted*
Results and discussion	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Abamectin

JUNE 2009

Document IIIA

Section 6: Toxicological and Metabolic Studies

From
Tier I - Section 3 - Annex II
of 91/414 dossier:
Toxicology and metabolism studies on the active substance

XXXXX parts that haven't been removed from the initial submission e.g Syngenta conclusions left to compare with RMS conclusions, justifications provided by Syngenta for non submission of studies

XXXXX parts that are present in abamectin PPP DAR and not in initial Syngenta submission

XXXXX slight changes in the text from abamectin PPP DAR and comments given for information

The study summaries presented in this Doc IIIA are completely based on the Abamectin 91/414/EEC Draft Assessment Report (DAR) issued October 2005 by the 91/414/EEC Rapporteur Member State The Netherlands (abamectin Vol. 3, B6 – Annex B – Tox section), and the abamectin addendum Vol. 3, B6 revised_February 2008. Abamectin has been evaluated for Plant Protection Products under 91/414/EEC and has been included in Annex I of 91/414/EEC (Commission Directive 2008/107/EC of 25 November 2008).
In a DAR for Plant Protection Products a summary of all studies is presented after a particular section (e.g. 'acute toxicity' or 'toxicokinetics'). In a CAR in Doc IIIA such a summary is normally not given, but since these summaries are available in the DAR for abamectin, these summaries are also presented in this CAR.

Abamectin (codes MK-0936 or CO76 B1) is comprised of two macrocyclic lactones avermectin B1a (≥80%) and avermectin B1b (≤20%), produced by the actinomycete *Streptomycetes avermetilis*. The two compounds vary only by the presence of a methylene group (avermectin B1a has a butyl- side chain and avermectin B1b has an isopropyl side chain). Avermectin B1a has a molecular weight of 873.
This evaluation contains studies performed with abamectin and studies performed with the 8,9-Z isomer of abamectin B1a (code name NOA 427011) (also referred to as the Δ-8,9 geometric isomer), a product of abamectin photolysis.
An important aspect to consider in the risk assessment of abamectin is the role of p-glycoprotein polymorphism and its relevance for human risk assessment. This is explained in '10. Mechanistic data'.

1. ACUTE TOXICITY

98/8 Doc IIIA section No.	6.1.1 / 01	Acute toxicity – Oral	Official use only
91/414 Annex Point addressed	II 5.2.1 / 01	Acute toxicity - oral	

Title:	MK 936 - Acute oral toxicity study in rats	
Lab Report Number:	No. TT 81-2937	
Authors:	[redacted]	
Test Substance:	Avermectin B1 technical grade ([redacted])	
Species:	Rat	
Guidelines:	OECD guideline no. 401 (February 1987) and 92/69/EEC B.1 with the following exception: Groups were not treated at constant volume, but at constant solution concentration	
Date of Report:	10 August 1981.	
Published:	No	
GLP:	Yes	

Characteristics

Reference/notifier	:	[redacted] (1981a)	Exposure	:	Once (by gavage)
Type of study	:	Acute oral toxicity study	Dose	:	6.67, 10, 15, 22.5 and 33.75 mg/kg bw
Year of execution	:	1981	Vehicle	:	Sesame oil
Test substance	:	Abamectin technical (purity [redacted])	GLP statement	:	yes
Route	:	Oral	Guideline	:	In accordance with OECD 401
Species	:	Rat, CRCD strain	Acceptability	:	Acceptable
Group size	:	10/sex/dose	LD50 rats	:	8.7 mg/kg bw (m), 12.8 mg/kg bw (f)

Study design

The study is in accordance with OECD 401, with the following deviations: the groups were not treated at constant volume, but at constant solution concentration, there is no information on housing conditions.

Results

Mortality: Death occured from 3 hours to 6 days in all groups of male rats (numbers of death males are 2, 7, 9, 9 and 9 in the different dose groups). No mortality was observed in females of the lowest dose group, whereas in the higher dose groups death occured from 5 hours to 5 days post-treatment (numbers of death females are 0, 1, 8, 10 and 10 in the different dose groups).
Symptoms of toxicity: Ataxia and whole body tremors occured in all dose groups within 3 hours after exposure. These signs persisted in male rats until day 6. Females of the 6.67 mg/kg bw group appeared normal on day 2, females treated at higher dose levels continued to show symptoms until day 4.
Body weight: normal in surviving animals
Pathology: no toxicologically relevant findings.

Acceptability

The study is considered acceptable.

Conclusions

The acute oral LD50 is 8.7 mg/kg bw for males and 12.8 mg/kg bw for females.

Reliability Indicator	1	
Data Protection Claim	Yes	

98/8 Doc IIIA section No.	6.1.1 / 02	Acute toxicity – Oral	Official use only
91/414 Annex Point addressed	II 5.2.1 / 02	Acute toxicity - oral	

Title:	Acute Oral Toxicity Study of Abamectin Technical in Rats.	
Lab Report Number:	No. 1039-00	
Authors:	[redacted]	
Test Substance:	Abamectin Technical; Batch [redacted]; Purity: [redacted].	
Species:	Rat	
Guidelines:	OECD Guideline 401	
Date of Report:	17.01.2001	
Published:	No	
GLP:	Yes	

Characteristics

Reference/notifier	:	[redacted] (2001)	Exposure	:	Once (by gavage)
Type of study	:	Acute oral toxicity study	Dose	:	20, 50, 100, 275 and 500 mg/kg bw
Year of execution	:	2000	Vehicle	:	Water (20 and 50 mg/kg bw), 0.5% w/v methylcellulose in water (100, 275 and 500 mg/kg bw)
Test substance	:	Abamectin (purity [redacted] avermectin B_{1a}, [redacted] avermectin B_{1B})	GLP statement	:	yes
Route	:	oral	Guideline	:	In accordance with OECD 401
Species	:	rat	Acceptability	:	acceptable
Group size	:	5/sex/dose	LD50 rats	:	232 mg/kg bw (m), 214 mg/kg bw (f)

Study design

The study is in accordance with OECD 401.

Results

Mortality: animals were found dead or were sacrified in a moribound condition within 9 days after dosing with 275 mg/kg bw (3 males and 4 females) and within 5 days after dosing with 500 mg/kg bw (5 males and 4 females).
Symptoms of toxicity: hypoactivity, staggered gait, dyspnea, wet around the mouth, lacrimation, thin appearance, hunched posture, cold to touch, prostration and tremors were observed in animals dosed 275 or 500 mg/kg bw. Surving animals had recovered by day 8 and day 6 in the 275 mg/kg bw and 500 mg/kg bw groups respectively.
Body weight: normal in surviving animals
Pathology: In the animals that died or were sacrificed in moribound condition, occular, nasal and/or oral discharges of variable consistency and perianal/perineum staining were observed. In the surviving animals no toxicologically relevant findings were observed.

Acceptability

The study is considered acceptable.

Conclusions

The acute oral LD50 is 232 mg/kg bw for males and 214 mg/kg bw for females.

Reliability Indicator	1	
Data Protection Claim	Yes	

98/8 Doc IIIA 6.1.1 / 03 section No.	Acute toxicity – Oral	Official use only
91/414 Annex II Point addressed 5.8.1 / 01	**Acute toxicity - oral**	

Title:	Two metabolites of MK-936 acute oral toxicity study in mice	
Lab Report Number:	No. TT 83-068-0	
Authors:	[redacted]	
Test Substance:	Abamectin photolysis metabolites L-652,871-00N01 (polar metabolite), and L-652,280-00N02 (non-polar metabolite) (purity unable to be quantified)	
Species:	Mouse	
Guidelines:	The test method employed meets the requirements of OECD guideline no. 401 (February 1987) and 92/69/EEC, B.1, with the exceptions: Dose levels of the 8,9-Z isomer of avermectin B1a were too low to produce toxicity. Groups were not treated at constant volume, but at constant solution concentration.	
Date of Report:	17 April 1984	
Published:	No	
GLP:	Yes	

In DAR : STUDY 1 (B6.8 Further tox studies, B.6.8.1 Toxicity studies of metabolites, B.6.8.1.1 Metabolite studies)

Characteristics

Reference/notifier	:	[redacted] (1984f)	Exposure	:	once
Type of study	:	Acute oral toxicity study in mice with two metabolites of MK-936 (abamectin).	Doses	:	1250, 2500 and 5000 mg/kg bw (polar testsubstance) 6, 12, 24 and 48 mg/kg bw (non-polar testsubstance)
Year of execution	:	1983	Vehicle	:	Methylcellulose, 1% (polar testsubstance) or sesame oil (non-polar testsubstance)
Test substances	:	Polar photodegradate of abamectin [redacted]) and 8,9-Z isomer of avermectin B1a [redacted]	GLP statement	:	yes
Route	:	Oral (gastric intubation)	Guideline	:	OECD 401
Species	:	Mice (CF-1)	Acceptability	:	Acceptable for the non-polar metabolite
Group size	:	5/sex/dose and 5 controls/vehicle	LD50 (polar metabolite) mice)	:	-
			LD50 (non-polar metabolite) mice)	:	> 48 mg/kg bw

1: The study author stated that the components of this polar metabolite have not been identified therefore it was not possible to assess purity and stability of the test article.

Study design

The study is in accordance with OECD 401, with the following deviation: the polar metabolite was given in a volume of 50 ml/kg bw, and the non-polar metabolite was given in a volume of 48 mg/kg bw; individual description of clinical signs and necropsy data were not included.

Results

POLAR METABOLITE

Mortality: none

Symptoms of toxicity: All mice showed decreased activity and bradypnea within 10 minutes of treatment and these symptoms persisted for approximately 4 h.

Body weight: normal

Pathology: no treatment-related changes.

NON-POLAR METABOLITE

Mortality: one male in the 12 mg/kg bw group died 4.5 h after treatment (cause of death was established as an intubation accident)

Symptoms of toxicity: decreased activity and bradypnea was observed prior to death in the male dosed 12

mg/kg bw.

Body weight: normal

Pathology: no treatment-related changes.

Acceptability

Since the components of the polar metabolite have not been identified and no information is available on the purity and stability of the test article, the results of the study with this component are less valuable. The study is considered acceptable for the non-polar metabolite.

Conclusions

The acute oral LD50 in CF-1 mice is > 48 mg/kg bw for the non-polar metabolite (8,9-Z isomer of Avermectin B1a).

Reliability Indicator	1	
Data Protection Claim	Yes	

98/8 Doc IIIA section No.	6.1.1 / 04	Acute toxicity – Oral	Official use only
91/414 Annex Point addressed	II 5.8.1 / 02	**Acute toxicity - oral**	

Title:	L-652,280-00N (8,9-isomer of MK-0936) acute oral toxicity study in mice	
Lab Report Number:	No. TT 84-112-0	
Authors:	[redacted]	
Test Substance:	8,9-Z isomer of Abamectin (batch no. [redacted], purity [redacted] by HPLC)	
Species:	Mouse	
Guidelines:	The test method employed generally exceeds the requirements of OECD guideline no. 401 (February 1987) and 92/69/EEC, B.1, with the following exception: The treatment volume administered was variable and, for the two highest dose levels, exceeded the maximum volume (10 ml/kg) for oil-based vehicles.	
Date of Report:	9 April 1986	
Published:	No	
GLP:	Yes	

In DAR : STUDY 2 (B6.8 Further tox studies, B.6.8.1 Toxicity studies of metabolites, B.6.8.1.1 Metabolite studies)

Characteristics

Reference/notifier	:	[redacted] (1986c)	Exposure	:	once
Type of study	:	Acute oral toxicity study in mice with the 8,9-Z isomer of MK-936 (avermectin B1a).	Doses	:	0, 5, 10, 20, 40 and 80 mg/kg bw

Year of execution	:	1984	Vehicle	:	sesame oil
Test substances	:	8,9-Z isomer of Avermectin B1a [redacted]	GLP statement	:	yes
Route	:	Oral (gastric intubation)	Guideline	:	OECD 401
Species	:	Mice (Crl:CF-1 (BR))	Acceptability	:	acceptable
Group size	:	10/sex/dose	LD50 mice	:	>80 mg/kg bw

Study design

The study is in accordance with OECD 401, with the following deviation: the treatment volume was variable and, for the two highest dose levels, exceeded the maximum volume of 10 ml/kg bw for oil-based vehicles.

Results

Mortality: mortality incidences were 0, 10, 10, 20, 0 and 30% in male groups and 0, 0, 10, 10, 0 and 10% in female groups, in order of ascending dose level. All deaths occured within 24 h of treatment.
Symptoms of toxicity: decreased activity, bradypnea, ataxia and ptosis occurred within 60-90 minutes of treatment in all treated groups except the females receiving 5 mg/kg bw. The symptoms persisted until day 2 in males of the 40 mg/kg bw group and in both sexes of the 80 mg/kg bw group.
Body weight: normal
Pathology: no treatment-related changes.

Acceptability

The study is considered acceptable.

Conclusions

The acute oral LD50 in CF-1 mice is > 80 mg/kg bw for the non-polar metabolite, the 8,9-Z isomer of Avermectin B1a.

Reliability Indicator	1	
Data Protection Claim	Yes	

98/8 Doc IIIA section No.	6.1.1 / 05	Acute toxicity – Oral	Official use only
91/414 Annex Point addressed	II 5.8.1 / 03	Acute toxicity - oral	

Title:	L-652,280: exploratory acute oral toxicity study in mice	
Lab Report Number:	No. TT 95-2754	
Authors:	[redacted]	
Test Substance:	8,9-Z isomer of Abamectin [redacted] purity not specified)	
Species:	Mice	
Guidelines:	Not applicable (in house investigative study)	
Date of Report:	20 February 1996	
Published:	No	
GLP:	No	

In DAR : STUDY 3 (B6.8 Further tox studies, B.6.8.1 Toxicity studies of metabolites, B.6.8.1.1 Metabolite studies)

Characteristics

Reference/notifier	:	[redacted] (1996)	Exposure	:	once
Type of study	:	Acute oral toxicity study in mice with the 8,9-Z isomer of MK-936 (avermectin B1a).	Doses	:	M (CF-1): 10, 20, and 30 mg/kg bw F (CD-1): 50, 90, 162, 290 and 525 mg/kg bw
Year of execution	:	1995	Vehicle	:	sesame oil
Test substances	:	8,9-Z isomer of avermectin B1a [redacted]	GLP statement	:	no
Route	:	Oral (gavage)	Guideline	:	unknown
Species	:	Mice (CF-1 and CD-1))	Acceptability	:	acceptable
Group size	:	3 groups of 5 m CF-1/dose and 5 groups of 3 f CD-1/dose.	LD50 CD-1 female mice)	:	217 mg/kg bw
			LD50 CF-1 male mice)	:	> 10 and < 20 mg/kg bw

Study design

Three groups of 5 fasted male CF-1 strain mice (approximately 14 weeks old) were treated once by gavage with the 8,9-Z isomer of avermectin B1a as a suspension in sesame oil at dose levels of 10, 20 and 30 mg/kg bw. Five groups of 3 fasted female CD-1 strain mice (7-8 weeks old) were similarily treated with the 8,9-Z isomer of avermectin B1a at dose levels of 50, 90, 162, 290 and 525 mg/kg bw. Clinical signs were recorded daily for 7 days and body weights were recorded pre-test and on day 7. Decedents and surviving animals (after killing) were discarded without necropsy. The LD50 value in female CD-1 mice was determined by the method of Weil. The LD50 value in male mice was estimated.

Results

CD-1 MICE

Mortality: All females treated at 290 and 525 mg/kg bw died within 2 days of treatment.

Symptoms of toxicity: prior to death, the animals treated at 290 and 525 mg/kg bw were moribund within 5 h of treatment and showed decreased activity, bradypnea and in some animals tremors on handling. In animals of the highest dose group urine staining was evident. Animals in the 162 mg/kg bw dose group showed decreased activity and bradypnea from day 2 to day 3 and hunched posture on day 3. Animals dosed 90 mg/kg bw showed decreased activity and unkemptness on day 2 only.

Body weight: normal

Pathology: not performed

CF-1 MICE

Mortality: In order of ascending dose levels there were 1/5, 3/5 and 2/5 deaths.

Symptoms of toxicity: decreased activity and bradypnea at all dose levels and ptosis at 30 mg/kg bw occured within 30 minutes of treatment. Decedents were moribund within 3 h of treatment and some animals treated at 20 or 30 mg/kg bw showed tremors on handling. Urine staining was evident at 30 mg/kg bw. Survivors were of normal appearance by day 2.

Body weight: normal

Pathology: not performed

Acceptability

The study is considered acceptable.

Conclusions

For the 8,9-Z isomer of Avermectin B1a, the acute oral LD50 in CD-1 female mice is 217 mg/kg bw, whereas the acute oral LD50 in CF-1 male mice is between 10 and 20 mg/kg bw.

SYNGENTA CONCLUSIONS

Conclusion:	The acute oral LD50 value of the 8,9-Z isomer of Abamectin in female CD-1 mice was calculated to be 217 mg/kg, and estimated to be 20 mg/kg in male CF-1 mice.	

Reliability Indicator	1	
Data Protection Claim	Yes	

98/8 Doc IIIA 6.1.1 / 06 section No.	Acute toxicity – Oral	Official use only
91/414 Annex Point addressed	II 5.8.2 / 02	Acute toxicity - oral

Title:	I. Acute oral toxicity studies with Abamectin (MK-0936) in pregnant and non-pregnant mice II. MK-0936 (L-676,863-00V50) five-day oral toxicity study in pregnant and non-pregnant CF-1 mice	
Lab Report Number:	No. TT 85-2593	
Authors:	[redacted]	
Test Substance:	Abamectin (MK-0936, batch no. [redacted], purity [redacted] by HPLC, avermectin B1 CO76 B1a + B1b)	
Species:	Mice	
Guidelines:	Not applicable (in house investigative study)	
Date of Report:	23 June 1986	
Published:	No	
GLP:	Yes	

In DAR : STUDY 3 (B.6.8 Further toxicological studies, B.6.8.2 Supplementary studies)

Characteristics

Reference/notifier	:	[redacted] (1986h)	Exposure	:	once
Type of study	:	Acute oral toxicity study with abamectin in pregnant and non-pregnant mice.	Doses	:	0, 5, 10, 20, 40 and 80 mg/kg bw
Year of execution	:	1985	Vehicle	:	sesame oil
Test substances	:	Abamectin technical (MK-0936, purity	GLP statement	:	yes

		[redacted], avermectin B1 CO76 B1a+B1b)			
Route	:	Oral (gastric intubation)	Guideline	:	Not applicable (in house investigative study)
Species	:	Mice (CF-1 strain)	Acceptability	:	acceptable
Group size	:	20 pregnant and 20 non-pregnant females/dose	LD50 non-pregnant mice	:	15.0 mg/kg bw
			LD50 pregnant mice	:	11.8 mg/kg bw

Study design

Six groups of female CF-1 strain mice each comprising 20 pregnant and 20 non-pregnant animals were treated by gastric intubation with a single oral dose of abamectin technical as a 0.2% solution in sesame oil, at dose levels of 0 (vehicle only), 5, 10, 20, 40 and 80 mg/kg bw. The animals were fasted for 2 hours before treatment. Pregnant animals were at day 10, 11 or 12 of gestation on the day of treatment. The animals were weighed pre-test and on day 5, observed for 1 - 2 hours after treatment and then daily for 5 days. All decedents and survivors were subjected to necropsy to confirm pregnancy status. The 5-day LD50 values and 95% fiducial limits were calculated by the method of probit analysis. The Mantel-Haenszel procedure was used to identify any significant difference in toxicity between pregnant and non-pregnant animals.

Results

Mortality: Deaths occurred in both pregnant and non-pregnant mice 36 minutes to 4 days after treatment (see table) and were preceded by loss of righting reflex.

Pregnancy status	Dose level (mg/kg)	No. dead / no. tested	Time of death	LD_{50} and fiducial limits (mg/kg)
Pregnant	5	6 / 20	45 min - 4 days	11.8 (8.3 - 15.8)
	10	5 / 19[a]		
	20	14 / 20		
	40	18 / 20		
	80	20 / 20		
	0 (vehicle)	0 / 20	-	-
Non-pregnant	5	3 / 20	36 min - 3 days	15.0 (10.2 - 21.1)
	10	9 / 20		
	20	11 / 20		
	40	15 / 20		
	80	19 / 20		
	0 (vehicle)	0 / 20	-	-

a: one animal was not pregnant

Symptoms of toxicity: Tremors, clonic convulsion and bradypnea occurred within 30 minutes of treatment in some pregnant mice at all dose levels. Tremors, bradypnea and decreased activity were apparent on days 2 and 3 at dose levels at and above 20 mg/kg bw. In non-pregnant mice, loss of righting reflex and bradypnea occured in some animals at all dose levels. Tremor was also apparent at dose levels at and above 10 mg/kg bw and ataxia at dose levels at and above 20 mg/kg bw.

Body weight: normal

Pathology: not performed

Acceptability

No individual data were included. The study is considered acceptable as investigative study.

Conclusions

The 5-day LD_{50} for abamectin technical in pregnant mice in this study, treated on day 10, 11 or 12 of gestation is 11.8 mg/kg bw, and the LD_{50} for abamectin technical in non-pregnant mice in this study is 15.0 mg/kg bw.

SYNGENTA CONCLUSIONS

Conclusion:	Based on a group size of 20 mice/dose level, the 5-day LD_{50} value in pregnant animals, 11.8 (8.3 - 15.8) mg/kg, was not statistically significantly lower than the LD_{50} value in non-pregnant animals, 15.0 (10.2 - 21.1) mg/kg. Therefore, the lower LD_{50} value in pregnant mice is considered not to represent a biologically meaningful difference.	

Reliability Indicator	1	
Data Protection Claim	Yes	

In DAR : **STUDY 2** (B.6.8 Further toxicological studies, B.6.8.2 Supplementary studies; this study summary is copied from the DAR for completeness, but is not present in the initial Doc IIIA from the notifier)

Characteristics

Reference/notifier	:	[redacted] (1986h)	Exposure	:	once
Type of study	:	Acute oral toxicity study with abamectin in pregnant and non-pregnant mice.	Doses	:	0, 5, 10, 20, 40 and 80 mg/kg bw

Year of execution	:	1985	Vehicle	:	sesame oil
Test substances	:	Abamectin technical (MK-0936, purity [redacted], avermectin B1 CO76 B1a+B1b)	GLP statement	:	yes
Route	:	Oral (gastric intubation)	Guideline	:	Not applicable (in house investigative study)
Species	:	Mice (CF-1 strain)	Acceptability	:	acceptable
Group size	:	12 pregnant and 10 non-pregnant females/dose	LD50 non-pregnant mice	:	>20 and <40 mg/kg bw
			LD50 pregnant mice	:	19.0 mg/kg bw

Study design

Six groups of female CF-1 strain mice each comprising 12 pregnant and 10 non-pregnant animals were treated by gastric intubation with a single oral dose of abamectin technical as a 0.2% solution in sesame oil, at dose levels of 0 (vehicle only), 5, 10, 20, 40 and 80 mg/kg bw. Pregnant animals were at day 10, 11 or 12 of gestation on the day of treatment. The animals were observed for about 2 h after treatment. The 5-day LD50 values and 95% fiducial limits were calculated by the method of probit analysis. The Mantel-Haenszel procedure was used to identify any significant difference in toxicity between pregnant and non-pregnant animals.

Results

Mortality: Deaths occurred in both pregnant and non-pregnant mice 73 minutes to 4 days after treatment (see table) and were preceded by loss of righting reflex.

Pregnancy status	Dose level (mg/kg)	No. dead / no. tested	Time of death	LD_{50} and fiducial limits (mg/kg)
Pregnant	5	0/12	73 min - 2 days	19.0 (14.0 – 25.7)
	10	2/12		
	20	7/12		
	40	10/12		
	80	12/12		
	0 (vehicle)	0 / 11[a]	-	-
Non-pregnant	5	2/10	83 min - 4 days	41.3 (-- - ---)[b] (conclusion study author)
	10	0/10		
	20	0/10		
	40	6/10		
	80	8/10		
	0 (vehicle)	0/10	-	-

a: one animal was not pregnant

b: no confidence limits given

Symptoms of toxicity: Within one hour of dosing tremors and bradypnea occurred at all dose levels in non-pregnant mice and at all but the lowest dose level in the pregnant group.

Body weight: normal

Pathology: not performed

Acceptability

No individual data were included. The reported LD_{50} in non-pregnant mice of 41.3 mg/kg bw by the study author is considered not reliable, since 6/10 animals died in the 40 mg/kg bw dose group.

The study is considered acceptable as investigative study.

Conclusions

The 5-day LD_{50} for abamectin technical in pregnant mice in this study, treated on day 10, 11 or 12 of gestation is 19.0 mg/kg bw, and the LD_{50} for abamectin technical in non-pregnant mice is not 41.3 mg/kg bw, as concluded by the study author, but >20 and <40 mg/kg bw.

98/8 Doc IIIA section No.	6.1.1 / 07	Acute toxicity – Oral	Official use only
91/414 Annex Point addressed	II 5.8.2 / 03	Acute toxicity - oral	

Title:	Abamectin exploratory acute oral toxicity study in mice	
Lab Report Number:	No. 96-2727	
Authors:	[redacted]	
Test Substance:	Abamectin (batch no. [redacted] purity not specified)	
Species:	Mice	
Guidelines:	Not applicable (in house investigative study)	
Date of Report:	21 March 1997	
Published:	No	
GLP:	No	

In DAR : STUDY 4 (6.8 Further toxicological studies/6.8.2 Supplementary studies)

Characteristics

Reference/notifier	:	[redacted] (1997)	Exposure	:	once
Type of study	:	Exploratory acute oral toxicity study in mice of known genotype for expression of P-glycoprotein.	Doses	:	0, 10, 20, 40 and 80 mg/kg bw
Year of execution	:	1996	Vehicle	:	sesame oil
Test substances	:	Abamectin technical (purity not specified)	GLP statement	:	no
Route	:	Oral	Guideline	:	Not applicable (in house investigative study)
Species	:	Mice (CF-1 strain)	Acceptability	:	acceptable
Group size	:	5 homozygous positive and 5 heterozygous females/dose	LD50 homozygous positive females for glycoprotein expression	:	28 mg/kg bw
			LD50 heterozygous females for glycoprotein expression	:	14 mg/kg bw

Study design

This study was conducted to compare the toxicity of abamectin after a single oral dose to female CF-1 strain mice previously identified as homozygous positive (+/+) or heterozygous (+/-) for P-glycoprotein expression.

Female CF-1 strain mice were genotyped as homozygous positive (+/+) or heterozygous (+/-) for P-glycoprotein expression by RFLP analysis using radiolabelled cDNA probes. The mice were divided into 5 groups each containing 5 homozygous positive and 5 heterozygous animals. Food was withdrawn for 2 hours and the animals were given a single oral dose of abamectin technical (purity not specified), in sesame oil, at dose levels of 0 (vehicle only), 10, 20, 40 or 80 mg/kg bw. Individual body weights were recorded pre-dose and on days 7 and 14 after dosing.

Clinical signs were recorded daily for 14 days. Vehicle control mice identified as homozygous positive were killed on day 14 and approximately 200 mg of the liver was removed and stored on dry ice (for possible future analysis). All remaining survivors were killed and discarded without necropsy on day 14. An approximate LD50 value was calculated for each genotypic population using the method of Weil.

Results

Mortality: All homozygous positive mice treated at 40 or 80 mg/kg bw (time of death 2-5 days and 0-2 days respectively) and all heterozygous mice treated at and above 20 mg/kg bw died (time of death 1-3 days at 20 mg/kg bw and 0-1 day at 40 and 80 mg/kg bw).

Symptoms of toxicity: tremors, decreased activity and bradypnea occurred in all abamectin-treated groups within a few hours of treatment and persisted for one to four days.

Body weight: homozygous positive animals treated at 20 mg/kg and heterozygous mice treated at 10 mg/kg bw showed transiently weight loss during the first week after treatment.

Pathology: not performed.

Acceptability

The study is considered acceptable as investigative study.

Conclusions

The approximate acute oral LD_{50} values in female CF-1 strain mice homozygous positive and heterozygous for P-glycoprotein expression are 28 mg/kg bw and 14 mg/kg bw, respectively.

SYNGENTA CONCLUSIONS

Conclusion:	The approximate acute oral LD_{50} values in female CF-1 strain mice homozygous positive and heterozygous for p-glycoprotein expression are 28 mg/kg and 14 mg/kg, respectively. Therefore, the homozygous positive genotype confers greater resistance to the lethal effects of Abamectin.	

98/8 Doc IIIA 6.1.1/ 08 section No.	Antidote study in dogs	Official use only
91/414 Annex II Point addressed 5.8.1	No corresponding annex point	
Title:	MK-0936 exploratory non-specific antidote study of MK-0936 intoxication in dogs	
Lab Report Number:	TT 84-085-0	
Authors:	[redacted] (1984h)	
Test Substance:	Abamectin technical (MK-0936, batch no. [redacted]	
Species:	Dogs	
Guidelines:	Not applicable (investigative study)	
Date of Report:	10 December 1984	
Published:	No	
GLP:	No	

In DAR : STUDY 9 (6.8 Further toxicological studies/6.8.2 Supplementary studies)

Characteristics

Reference/notifier	:	[redacted] (1984h)	Exposure	:	15 minutes
Type of study	:	Exploratory non-specific antidote study of abamectin intoxication in dogs.	Doses	:	8.0 mg/kg bw
Year of execution	:	1984	Vehicle	:	Sesame oil
Test substances	:	Abamectin technical (MK-0936, purity [redacted])	GLP statement	:	no
Route	:	Oral (gavage)	Guideline	:	Not applicable (in house investigative study)
Species	:	Beagle dogs	Acceptability	:	acceptable
Group size	:	2/sex/time point of antidote treatment			

Study design

Initially, 6 groups of 2 male and 2 female beagle dogs were treated with a single oral dose (by gavage) of 8 mg/kg bw abamectin technical in sesame oil, followed by gavage treatment with 30 ml ipecac or 3g charcoal as a slurry in at least 30ml water, 0.5, 1.0 or 2.0 hours post-treatment. A further group of 4 animals received 8 mg/kg bw abamectin only. Since none of the treatments were effective, two further groups were treated with a single gavage dose of 8 mg/kg bw abamectin followed by ipecac at 15 minutes post-treatment (7 animals), or by ipecac at 15 minutes and charcoal at 30 minutes post-treatment (14 animals).

Specific clinical signs, were recorded on 16 occasions during the 8 hours immediately following treatment and twice daily thereafter until no clinical signs were apparent. Food consumption was estimated daily and body weights were recorded twice weekly until no clinical signs were apparent. No other investigations were performed.

Results

Ipecac or charcoal administered 30 minutes, 1 or 2 h post-treatment had no effect on the onset, severity and duration of mydriasis, emesis, ataxia, tremors, convulsions and coma, mortality and the time of death. The administration of ipecac 15 minutes post-treatment reduced mortality and the incidence and duration of mydriasis, ataxia, tremors, convulsions and coma, compared with groups not receiving ipecac at 15 minutes post-treatment. There were no treatment-related deaths or coma in the animals treated with ipecac at 15 minutes, whereas 38% of animals not receiving ipecac at 15 minutes were comatose and died within 2-72 h of treatment. Emesis occurred in all animals treated with ipecac at 15 minutes within 10 - 55 minutes of treatment. Abamectin also induced emesis but generally later and less predictably. Mydriasis occurred in all but one animal in each of the combined groups but the time of onset was delayed for up to 5 hours and the duration was markedly reduced when ipecac was administered within 15 minutes (mean 1.75 days), compared with the other animals (mean 5.0 days). Ataxia occurred at reduced incidence in animals treated with ipecac at 15 minutes (52% vs. 79%) and with delayed onset (2.25 hours vs. 1.75 hours) and shorter duration (2.0 days vs. 3.0 days). Tremors and convulsions also occurred at reduced incidence in animals treated with ipecac at 15 minutes (14% vs. 45% for tremors, 10% vs. 24% for convulsions). There were no treatment-related effects on food consumption and body weight during the 2-week observation period that distinguished animals treated with ipecac at 15 minutes from those treated under other regimens.

Acceptability

The study is considered acceptable as exploratory study.

Conclusions

Ipecac administered within 15 minutes of ingestion of 8 mg/kg bw abamectin technical prevented coma and death and reduced the incidence and/or severity and/or duration of typical clinical signs of abamectin intoxication (mydriasis, ataxia, tremors and convulsions). Administration of charcoal and ipecac administered more than 15 minutes after abamectin technical ingestion are ineffective in reducing abamectin-induced toxicity.

Reliability Indicator	1	
Data Protection Claim	Yes	

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	*5 November 2007; updated January 2009*
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion. Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*

Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

98/8 Doc IIIA section No.	6.1.2 / 01	Acute toxicity – Dermal	Official use only
91/414 Annex Point addressed	II 5.2.2 / 01	Acute toxicity - percutaneous	

Title:	CO76 B1 acute dermal toxicity study in rats	
Lab Report Number:	No. TT 78-3607	
Authors:	[redacted]	
Test Substance:	Abamectin (CO76 B1, batch no. [redacted] B1a and [redacted] B1b) wetted with saline	
Species:	Rat	
Guidelines:	OECD guideline 402 and 92/69/EEC B.3 with the following exceptions: Limit dose employed was 330 mg/kg, not 2000 mg/kg. Test article was not removed from the application site after 24 hours exposure. Survivors were not subjected to necropsy at the end of the study.	
Date of Report:	22 March 1985	
Published:	No	
GLP:	No	

Characteristics

Reference/notifier	:	[redacted] (1985a)	Exposure	:	24 h
Type of study	:	Acute dermal toxicity study, limit test	Dose	:	330 mg/kg bw
Year of execution	:	1978	Vehicle	:	saline
Test substance	:	Abamectin technical (purity [redacted])	GLP statement	:	no
Route	:	Dermal	Guideline	:	-
Species	:	Rat (Crl:CD(SD)BR)	Acceptability	:	acceptable
Group size	:	5/sex	LD50 rats	:	>330 mg/kg bw

Study design

The study is in accordance with OECD 402, with the following deviations: the limit dose was 330 mg/kg bw instead of 2000 mg/kg bw, the test substance was not removed from the application site after 24h exposure, necropsy was not performed, there is no information on housing conditions.

Results

Mortality: none

Symptoms of toxicity: on day 3 tremors and ataxia were observed in 8 animals, and on day 4 decreased activity was also apparent. On day 8 all animals were recovered.

Body weight: weight losses were observed in 6 animals during the first week and in two animals in the second week after exposure.

Pathology: not performed

Acceptability

The study is considered acceptable.

Conclusions

The acute dermal LD_{50} in rats is >330 mg/kg bw.

Reliability Indicator	1	
Data Protection Claim	Yes	

98/8 Doc IIIA section No.	6.1.2 / 02	Acute toxicity – Dermal	Official use only
91/414 Annex Point addressed	II 5.2.2 / 02	Acute toxicity - percutaneous	

Title:	MK-0936 technical material acute dermal toxicity study in rabbits	
Lab Report Number:	No. 83-064-0	
Authors:	[redacted]	
Test Substance:	Technical grade MK-0936, batch no. [redacted], purity [redacted])	
Species:	Rabbits	
Guidelines:	The method used is a limit test performed according to OECD guideline 402 (February 1987) and 92/69/EEC B.3; no deviations	
Date of Report:	29 June 1984	
Published:	No	
GLP:	Yes	

Characteristics

Reference/notifier	:	[redacted] (1984a)	Exposure	:	24 h
Type of study	:	Acute dermal toxicity study, limit test	Dose	:	2120 mg/kg bw
Year of execution	:	1983	Vehicle	:	saline
Test substance	:	Abamectin technical (purity [redacted])	GLP statement	:	yes
Route	:	dermal	Guideline	:	-
Species	:	Rabbit	Acceptability	:	acceptable
Group size	:	5/sex	LD50 rabbit	:	>2000 mg/kg bw

Study design

The study is in accordance with OECD 402, with the following deviation: there is no information on housing conditions.

Results

Mortality: none

Symptoms of toxicity: within 6 days 9 animals showed lethargy, bradypnea, tremors, ataxia, abnormal head movements and disorientation, and by day 13 all animals were similarly affected.

Body weight: all animals showed progressive weight loss (weight loss of 21-37% of their initial body weight at termination).

Pathology: reddened areas in the colonic or gastric mucosa.

Acceptability

The study is considered acceptable.

Conclusions

The acute dermal LD_{50} in rabbits is >2000 mg/kg bw.

Reliability Indicator	1	
Data Protection Claim	Yes	

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	*5 November 2007; updated January 2009*
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	
	COMMENTS FROM ...
Date	*Give date of comments submitted*

Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion. Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	