European Commission

Addendum

VOLUME 3 – Annex B (A12115l)

Abamectin

B.6 Toxicology and metabolism

Rapporteur Member State: The Netherlands

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Draft Assessment Report and Proposed decision of the Netherlands prepared in the context of the possible extension of the approval conditions of abamectin under Regulation (EC) 1107/2009

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B.6 Toxicology and metabolism data

A12115I is a suspension concentrate (SC) containing 20 g/l abamectin for use on vegetables grown indoors. This formulation was not the representative formulation in the original EU review of abamectin.

B.6.1 Acute toxicity

A12115I containing 20 g/L abamectin has a low toxicity in respect of acute oral, dermal and inhalation toxicity and is not irritating to the rabbit skin or eye and is not a skin sensitiser. The classification according to Regulation (EC) 1272/2008 as amended, is given in the table below.

Table B.6.1-1: Summary of acute toxicological data obtained with A12115I

Parameter [Reference]	Species	Result	Classification according to Regulation (EC) 1272/2008 as amended
Acute oral MLD [redacted 2009a]	Rat	LD_{50} = 1086 mg/kg (female)	Acute Tox. 4, H302 (Harmful if swallowed)
Acute dermal MLD [redacted 2010]	Rat	LD_{50} > 5000 mg/kg	No classification
Acute inhalation MLC [redacted 2009]	Rat	LC_{50} >1.02mg/L	Acute Tox. 4, H332 (Harmful if inhaled)
Acute skin irritation [redacted 2009b]	Rabbit	Not irritant	No classification
Acute eye irritation [redacted 2009c]	Rabbit	Slightly irritating	No classification
Skin sensitisation [redacted 2009d]	Guinea Pig	Not a sensitiser (modified Buehler)	No classification

B.6.1.1 Oral

reference	:	[redacted] 2009a	exposure	:	Oral gavage
Report number	:	Syngenta File No.A121151/10020	doses	:	2000 mg/kg bw, 550 mg/kg bw, 175 mg/kg bw
test substance		Abamectin SC (A12115I)	GLP statement	:	yes
species	:	Rat, Wistar	guideline	:	in accordance with OECD 425.
			acceptability	:	acceptable

STUDY DESIGN

Materials:

Test Material:	**Abamectin SC (A12115I)**
Description:	Liquid; black

Test Material:	**Abamectin SC (A12115I)**
Lot/Batch number:	SMU9AL002
Purity:	19.4 g/l corresponding to 1.619% w/w
CAS#:	Not available
Stability of test compound:	Stable under storage conditions. Retest date: End of January 2012

Test Animals:	
Species:	Rat
Strain:	RccHan: WIST(SPF)
Age/weight at dosing:	11 weeks /182.1 g – 199.7 g body weight
Source:	[redacted]
Housing:	Individually in Makrolon type-3 cages with standard softwood bedding ('Lignocel' J. Rettenmaier&Söhne GmbH&CoKG, 73494 Rosenberg / Germany, imported by Provimi Kliba AG, 4303 Kaiseraugst / Switzerland)

Methods:

In-life dates: 13 May 2009 - 21 July 2009

Animal assignment and treatment: The animals received a single dose of the test item by oral gavage administration after being fasted for approximately 18 hours, but with free access to water. Food was presented approximately 3 to 4 hours after dosing. Dosing started in one female animal at a dosage level of 2000 mg/kg. The application volume was 1.67 mL/kg body weight. Since the animal had to be killed in extremis 3 hours after treatment, a main test was performed by dosing the next female animal at a dosage level of 175 mg/kg (application volume 0.146 mL/kg body weight). The dosage was continued in nine further animals at doses of 550 and 2000 mg/kg by using the Up and Down procedure. The application volume was 0.46 mL/kg and 1.67 mL/kg body weight, respectively. The animals were examined daily during the acclimatization period and mortality, viability and clinical signs were recorded. All animals were examined for clinical signs within the first 30 minutes and at approximately 1, 2, 3 and 5 hours after treatment on day 1 and once daily during test days 2-15. Mortality/viability was recorded once during the first 30 minutes and at approximately 1, 2, 3 and 5 hours after administration on test day 1 (with the clinical signs) and twice daily during days 2-15. Body weights were recorded on day –1 (prior to removal of food), day 1 (prior to administration) and on days 8 and 15. All animals were examined macroscopically after being killed at the end of the study.

Statistics: The oral LD_{50} was calculated using the Acute Oral Toxicity (OECD Test Guidelines 425) Statistical Programme (AOT 425 Stat Pgm); version: 1.0, 2001 was used for the selection of dose levels and calculation of the LD_{50} values.

RESULTS

Mortality: Four out of the six animals treated at 2000 mg/kg were killed in extremis approximately 3 hours after treatment or on test day 4. One out of six animals treated at 2000 mg/kg was found dead on test day 2. The remaining animal of this dosage level survived until the end of the study. All animals treated at 550 mg/kg and the only animal treated at 175 mg/kg survived until the end of the study.

Table B.6.1.1-1: Acute oral toxicity of abamectin SC (A12115l) in the rat, application scheme and mortality data

Animal Number	Dose [mg/kg body weight]	Volume given [mL/kg body weight]	Survival
1	2000 (limit-test)	1.67	Killed in extremis
2	175	0.146	Survived
3	550	0.46	Survived
4	2000	1.67	Killed in extremis
5	550	0.46	Survived
6	2000	1.67	Killed in extremis
7	2000	1.67	Found dead on test day 2
8	550	0.46	Survived
9	2000	1.67	Killed in extremis
10	550	0.46	Survived
11*	2000	1.67	Survived

*The stopping criteria were already met after the animal No. 10. It was unnecessary to dose the animal No. 11.

Clinical observations: Five out of six animals treated at 2000 mg/kg, which were killed in extremis or found dead, were noted with similar clinical signs between the 1- or 2-hour reading and the time they were killed or found dead. These include slightly to moderately ruffled fur, slight to moderate poor coordination, slight to marked tremor, hunched posture and slight to moderate sedation. Two of the five animals were also noted with black brown faeces or vocalization when touched. One out of six animals treated at 2000 mg/kg was observed with slightly ruffled fur at the 1-hour reading. From the 2-hour reading to test day 8 the animal was noted with slightly ruffled fur, hunched posture and/or slight poor coordination, slight sedation. From test day 9 to 15 the animal was still observed with slightly ruffled fur.

All four animals treated at 550 mg/kg were observed with mild form of clinical signs including slightly to moderately ruffled fur, slight poor coordination, hunched posture, slight sedation and slight tremor at the 5-hour reading (animal No. 3), from the 2-hour reading to test day 5 (animal No. 5), from the 3-hour reading to test day 2 (animal No. 8) and from the 3-hour reading to test day 4). All four animals survived until the end of the study.

Bodyweight: One animal treated at 2000 mg/kg (No. 11) exhibited a negligible body weight loss (-1.4%) from test day 1 to 8. The body weight of the animals was otherwise within the range commonly recorded for this strain and age.

Necropsy: Two animals treated at 2000 mg/kg which were killed in extremis 3 hours after treatment (animal Nos. 1 and 9) were recorded with dark brown contents in the stomach and the gastric

intestinal tract at necropsy. One of the animals (No. 1) was also noted with light brown kidneys. No macroscopic findings were recorded in the other nine animals at necropsy.
Animal No. 11 was incorrectly dosed at 2000 mg/kg, as the stopping criteria was already met with animal No. 10. Therefore this animal is not taken into consideration in the calculation of the MLD for this study.

CONCLUSION

The LD_{50} of abamectin SC (A12115I) after single oral administration to female rats, observed over a period of 14 days is 1086 mg/kg body weight (based on an assumed sigma of 0.5). The approximate 95% confidence interval is 550 to 2000 mg/kg body weight.

The acute oral LD_{50} was less than 2000 mg/kg, but greater than 200 mg/kg, therefore a classification of Acute Tox. 4, H302 (Harmful if swallowed) is required for acute oral toxicity of A12115I according to Regulation (EC) 1272/2008 as amended.

B.6.1.2 Dermal

reference	:	[redacted], 2010	exposure	:	Dermal, semi-occlusive
Report number	:	Syngenta File No. A12115I/10021	doses	:	5000 mg/kg bw
test substance		Abamectin SC (A12115I)	GLP statement	:	yes
species	:	Rat, Wistar	guideline	:	in accordance with OECD 402.
group size	:	5/sex	acceptability	:	acceptable

STUDY DESIGN

Materials:

Test Material:	**Abamectin SC (A12115I)**
Description:	Black liquid
Lot/Batch number:	SMU9AL002
Purity:	19.4 g/l corresponding to 1.619% w/w
CAS#:	Not available
Stability of test compound:	Stable under storage conditions. Retest date: 31-Jan-2012

Test Animals:	
Species	Rat
Strain	RccHan:WIST (SPF)
Age/weight at dosing	9-11 weeks / 197.0 – 268.2 g body weight
Source	[redacted]
Housing	During acclimatization in groups of five per sex in Makrolon type-4 cages with standard softwood bedding. Individually in Makrolon type-3

Test Animals:	
	cages with standard softwood bedding('Lignocel' J. Rettenmaier&Söhne GmbH&CoKG, 73494 Rosenberg / Germany, imported by Provimi Kliba AG, 4303 Kaiseraugst / Switzerland) during treatment and observation.

Methods:

In-life dates: 19 January 2010 - 11 February 2010

Animal assignment and treatment: A group of one male and one female and a second group of four male and four female RccHan:WIST (SPF) rats were treated with abamectin SC (A12115I) at 5000 mg/kg by dermal application. The test item was applied undiluted as delivered from the sponsor at a volume of 4.18 mL/kg. The application period was 24 hours.

One day before treatment, the backs of the animals were clipped with an electric clipper, exposing an area of approximately 10 % of the total body surface. Only those animals without injury or irritation on the skin were used in the test. On test day 1, the test item was applied evenly on the intact skin and was covered with a semi-occlusive dressing. The dressing was wrapped around the trunk and fixed with an elastic adhesive bandage. Twenty-four hours after the application the dressing was removed and the skin was flushed with lukewarm tap water and dried with disposable paper towels. Thereafter, the reaction sites were assessed.

The animals were examined daily during the acclimatization period concerning viability/ mortality and clinical signs. After treatment they were examined within the first 30 minutes and at approximately 1, 2, 3 and 5 hours after administration on test day 1 for local and clinical signs as well as viability/mortality. On test days 2 to 15 local and clinical signs were recorded once daily and viability/mortality twice daily. The body weights were recorded on test days 1 (prior to administration), 8 and 15. All animals were examined macroscopically after being killed at the end of the study.

RESULTS

Mortality: No intercurrent deaths occurred during the course of the study.

Table B.6.1.2-1: Acute dermal toxicity of abamectin SC (A12115I) in the rat (mortality data)

Dose Level	Day Number	Number of Deaths	
(mg/kg)		Male	Female
5000	1	0	0
	Total at day 15	0/5	0/5

Clinical and local observations: All animals survived until the end of the observation period. No clinical signs were during the course of the study.

A slight to marked brown staining produced by the test item was observed on test day 2 at the removal of the 24-hour semi-occlusive dressing. Therefore, the presence of a possible erythema was not assessable in nine out of ten treated animals (5 males, 4 females) which were observed with the marked brown staining. When assessable, no local findings were noted. The brown staining was

present from test day 2 to 5 (4 males and 2 females), 7 (1 male and 1 female), 8 (1 female) or 15 (1 female).

Body weight: The bodyweight of the animals was within the range commonly recorded for this age and strain.

Necropsy: No macroscopic findings were observed at necropsy.

CONCLUSION

The LD_{50} of abamectin SC (A12115I) after single dermal administration to rats of both sexes, observed over a period of 14 days post treatment is greater than 5000 mg/kg body weight.

The acute dermal LD_{50} was greater than 2000 mg/kg therefore no classification is required for acute dermal toxicity of A12115I according to Regulation (EC) 1272/2008 as amended.

B.6.1.3 Inhalation

reference	:	[redacted] 2009	exposure	:	Inhalation, nose-only
Report number	:	Syngenta File No. A12115I_10011	doses	:	1.1 mg/L
test substance	:	Abamectin SC (A12115I)	GLP statement	:	yes
species	:	Rat, Wistar	guideline	:	in accordance with OECD 403.
group size	:	5/sex	acceptability	:	acceptable

STUDY DESIGN

Materials:

Test Material:	**Abamectin SC (A12115I)**
Description:	Black liquid
Batch number:	SMU9AL002
Purity:	19.4 g/L, 1.62% w/w
CAS#:	Not available
Stability	Expiry: January 2012

Test Animals:	
Species	Rat
Strain	Crl:WI (HAN)
Age/weight at dosing	Young adult; 12-13 weeks 239-260 g (males); 192-211 g (females)
Source	[redacted]
Housing	Up to 5/sex per cage

Methods:

In-life dates: 19 February 2009 - 27 March 2009

Generation of the test atmosphere / chamber description: The test aerosol was generated from a 50% (v/v) solution of Abamectin SC (A12115I) in deionised water using a Sachsse jet atomiser into a flow-through (nose-only) exposure chamber (volume approximately 40 L) continuously for the duration of the exposure. The chamber was exhausted from the bottom of the chamber to ensure a dynamic flow of fresh aerosol through the chamber during exposure. The air flow rate through the atomiser and the exhaust rate were 28 L air/minute, monitored periodically during exposure, at normal temperature and pressure. Trial generations were carried out prior to the start of the study in order to determine the appropriate generation system and conditions required to achieve the target aerosol concentration and to ensure it remained stable and respirable throughout exposure.
The achieved aerosol concentration in the exposure chamber was measured gravimetrically at approximately half-hourly intervals throughout the exposure. A known volume of aerosol from the exposure chamber was sampled (ca 1 L/min), from an exposure port representative of that from which the animals were exposed, on to weighed glass-fibre filters. After sampling the filters were allowed to dry at room temperature and then weighed.
By weighing the test article reservoir before and after exposure and together with the total volume of air into which the test article was generated, the nominal aerosol concentration to which the animals were exposed was determined.
The particle size distribution (MMAD) of the aerosol was measured gravimetrically using a Marple 298 Cascade Impactor by sampling the aerosol from inside the chamber at a flow rate of 2 L/min approximately hourly. The data were transformed using a log/probit transformation and a linear regression derived from the cumulative data. The linear regression line was then used to calculate the mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD).

Animal assignment and treatment: Prior to the start of the study each animal was examined to ensure that it was physically normal and exhibited normal activity. Throughout exposure the clinical condition of each animal was observed and at the end of the 4-hour exposure period, each animal was given a detailed clinical examination. Animals were also subjected to detailed clinical observations, daily during the 14-day observation period. The body weight of each rat was recorded on days 1 (prior to exposure and immediately after exposure), 2, 3, 4, 8, 11, 15 and prior to termination on day 16. All animals were killed on day 16 and subjected to a gross examination post mortem involving external observation and careful internal examination of all thoracic and abdominal viscera.

RESULTS

Mortality: There was no mortality during the study.

Clinical observations: Red/brown staining was observed in all animals due to exposure to the test material. This was generally observed around the head, snout and dorsal region.
Dyspnoea was recorded in one male and one female in the final hour of exposure. Unkempt appearance, wet and thinning fur was also recorded in a number of animals.

Body weight: All animals lost weight following exposure. Four out of five males gained weight from day 2 onwards. All females gained weight on day 2 but several individuals lost weight on subsequent days. All females gained weight by day 16 compared with day 2 body weights. Mean body weight gains increased from day 2 onwards.

Necropsy: No macroscopic abnormalities were apparent at necropsy.

Analytical measurements: The exposure conditions are summarized in Table 6.1.3-1.

Table B.6.1.3-1: Technical data from the exposure to Abamectin SC (A12115I)

Parameter	Target concentration 1.1 mg/L
Gravimetric concentration	1.02 ± 0.104 mg/L
Nominal concentration	10.01 mg/L
Particle size MMAD; GSD	3.06 µm; 1.99
Particles > 21.3 µm (% w/w)	0.00 %
Particles 21.3-14.8 µm (% w/w)	1.45 %
Particles 14.8-9.8 µm (% w/w)	1.46 %
Particles 9.8-6.0 µm (% w/w)	14.24 %
Particles 6.0-3.5 µm (% w/w)	22.97 %
Particles 3.5-1.55 µm (% w/w)	45.05 %
Particles 1.55-0.93 µm (% w/w)	10.76 %
Particles 0.93-0.52 µm (% w/w)	3.78 %
Particles ≤0.52 µm (% w/w)	0.29 %
Flow rate (whole system)	28 L/min
Flow rate (individual tube)	2..8 L/min
Temperature	19.6 – 19.8°C (n=4)
Humidity	46.3 – 56.6% (n=4)
Oxygen content	20.6 % (n=4)

CONCLUSION

A single 4 hour inhalation (nose only) exposure to Abamectin SC (A12115I) at a mean atmospheric exposure level of 1.02 mg/L and within the respirable range for rats was generally well tolerated. No animals died or showed persistent adverse clinical signs. The LC_{50} is therefore considered to be in excess of 1.02 mg/L.

A classification of Acute Tox. 4, H332 (Harmful if inhaled) is required for acute oral toxicity of A12115I according to Regulation (EC) 1272/2008 as amended.

B.6.1.4 Skin irritation

reference : [redacted], 2009b exposure : Dermal, semi-occlusive

Report number	:	Syngenta File No. A121151/10015	doses	:	0.5 ml/animal
test substance	:	Abamectin SC (A12115I)	GLP statement	:	yes
species	:	Rabbit, New Zealand white	guideline	:	in accordance with OECD 404.
group size	:	3	acceptability	:	acceptable

STUDY DESIGN

Materials:

Test Material:	**Abamectin SC (A12115I)**
Description:	Liquid; black
Lot/Batch number:	SMU9AL002
Purity:	19.4 g/l corresponding to 1.619% w/w
CAS#:	Not available
Stability of test compound:	Stable under storage conditions. Retest date: End of January 2012

Test Animals:	
Species	Young adult New Zealand white rabbit, SPF
Age/weight at dosing	15 weeks / 2263 - 2475 g
Source	[redacted]
Housing	Individually in stainless steel cages equipped with feed hoppers and drinking water bowls. Wood blocks (Harlan Laboratories Ltd., Füllinsdorf) and haysticks 4642 (batch no. 69/08, Provimi Kliba AG) were provided for gnawing.

Methods:

In-life dates: 27 May 2009 – 24 Jun 2009

Animal assignment and treatment: The primary skin irritation potential of abamectin SC (A12115I) was investigated. Four days before treatment, the left flank was clipped with an electric clipper, exposing an area of approximately 10 cm x 10 cm. The skin of the animals was examined one day before treatment, and re-grown fur of all animals was clipped again. Animals with overt signs of skin injury or marked irritation which may have interfered with the interpretation of the results were not used in the test.

The test item was applied by topical semi-occlusive application of 0.5 mL to the intact left flank of each of three young adult New Zealand White rabbits. The duration of treatment was four hours. The scoring of skin reactions was performed 1, 24, 48 and 72 hours, as well as 7, 10, 14, 17 and 21 days after removal of the dressing.

On the day of treatment, 0.5 mL of abamectin SC (A12115I) was placed on a surgical gauze patch (approximately 2.5 cm x 2.5 cm). This gauze patch was applied to the intact skin of the clipped area. The patch was covered with a semi-occlusive dressing. The dressing was wrapped around the abdomen and anchored with tape.

The duration of treatment was 4 hours. Then the dressing was removed and the skin was flushed with lukewarm tap water to clean the application site so that any reactions (erythema) were clearly visible at that time.
As it was suspected that the test item might produce irritancy, a single animal was treated first. As no corrosive effect was observed after the 4-hour exposure, the test was completed using the two remaining animals for an exposure period of four hours.
The animals were checked daily for signs of systemic toxicity and mortality. The skin reaction was assessed according to the numerical scoring system listed in the Commission Directive 2004/73/EC, April 29, 2004, approximately 1, 24, 48 and 72 hours after the removal of the dressing, gauze patch and test item.

RESULTS

No clinical signs of systemic toxicity were observed in the animals during the study and no mortality occurred. The bodyweights of all rabbits were considered to be within the normal range of variability.
The mean score was calculated across 3 scoring times (24, 48 and 72 hours after patch removal) for each animal for erythema/eschar grades and for oedema grades, separately.
The mean erythema/eschar score of the three animals was 0.67, 0.00 and 0.67, respectively and the mean oedema score was 0.00 for each of the three animals.
A very slight erythema was observed in all treated animals 1 hour after test item exposure and persisted as very slight up to the 48- hour reading in one male and one female.
The test item caused slight brown staining of the treated skin in all animals and persisted up to the 14 days (one male) or 21 days (two females) after application. No corrosive effects were noted on the treated skin of any animal at any of the measuring.

Table B.6.1.4-1: Individual and mean skin irritation scores of abamectin SC (A12115I) according to the Draize scheme

Time	Erythema			Oedema		
Animal number	16	17	18	16	17	18
after 1 hour	1	1	1	0	0	0
after 24 hours	1	0	1	0	0	0
after 48 hours	1	0	1	0	0	0
after 72 hours	0	0	0	0	0	0
mean score 24-72 h	0.67	0	0.67	0	0	0
after 7 days	0	0	0	0	0	0
after 10 days	0	0	0	0	0	0
after 14 days	0	0	0	0	0	0
after 17 days	0	0	0	0	0	0
after 21 days	0	0	0	0	0	0

Note: Observations continued after the 72-hour reading s due to the brown staining present on the skin.

CONCLUSION

The application of abamectin SC (A12115I) to the intact skin resulted in mild, early-onset sign of irritation in all three animals.

The mean irritation scores 24 to 72 hours after application were less than the thresholds defined in Regulation (EC) 1271/2008. Therefore, according to Regulation (EC) 1271/2008 as amended, no classification is required for skin irritating properties of A12115I.

B.6.1.5 Eye irritation

reference	:	[redacted], 2009c	exposure	:	Instillation in eye
Report number	:	Syngenta File No. A121151/10016	doses	:	0.1 ml/animal
test substance	:	Abamectin SC (A12115I)	GLP statement	:	yes
species	:	Rabbit, New Zealand White	guideline	:	in accordance with OECD 405.
group size	:	3	acceptability	:	acceptable

STUDY DESIGN

Materials:

Test Material:	**Abamectin SC (A12115I)**
Description:	Liquid; black
Lot/Batch number:	SMU9AL002
Purity:	19.4 g/l corresponding to 1.619% w/w
Density:	1197 kg/m^3
CAS#:	Not available
Stability of test compound:	Stable under storage conditions. Retest date: 31-Jan-2012

Test Animals:	
Species:	Young adult New Zealand white rabbit, SPF
Age/weight at dosing:	13 weeks / 2171 - 2343 g
Source:	[redacted]
Housing:	Individually in stainless steel cages equipped with feed hoppers and drinking water bowls. Wood blocks (Harlan Laboratories Ltd., Füllinsdorf) and haysticks 4642 (batch no. 69/08, Provimi Kliba AG) were provided for gnawing.

Methods:

In-life dates: 10 Jun 2009 – 19 Jun 2009

Animal assignment and treatment: The primary eye irritation potential of abamectin SC (A12115I) was investigated. The test item was applied by instillation of 0.1 mL into the left eye of each of three

young adult New Zealand White rabbits. Scoring of irritation effects was performed approximately 1, 24, 48 and 72 hours after test item instillation.
On the day of treatment, 0.1 mL of abamectin SC (A12115I) was placed in the conjunctival sac of the left eye of each animal after gently pulling the lower lid away from the eyeball. The lids were then gently held together for about one second to prevent loss of test item. The right eye remained untreated and served as the reference control. The treated eyes were not rinsed after instillation.
As it was suspected that the test item might produce irritancy, a single animal (one female) was treated first. As neither a corrosive effect nor a severe irritant effect was observed after the 1- and 24-hour examinations, the test was completed using the two remaining animals.
The ocular reaction (i.e. corneal opacity, iridic effects, conjunctivae and chemosis) was assessed according to the numerical scoring system listed in the Commission Directive 2004/73/EC, April 29, 2004, at approximately 1, 24, 48 and 72 hours after test item instillation.

RESULTS

No clinical signs of systemic toxicity were observed in the animals during the study and no mortality occurred. The body weights of the rabbits were considered to be within the normal range of variability.
The mean score was calculated across 3 scoring times (24, 48 and 72 hours after instillation) for each animal for corneal opacity, iris, redness and chemosis of the conjunctivae, separately.
The individual mean scores for corneal opacity and iris were 0.00 for all three animals. The individual mean scores for the conjunctivae were 0.00 for reddening and 0.00 for chemosis in all three animals.
The instillation of abamectin SC (A12115I) into the eye of the three animals resulted in a slight redness of the conjunctivae 1 hour after instillation. A slight swelling was noted in both females at the 1-hour observation. Additionally, the sclera of the three animals was slightly reddened 1 hour after treatment and the slight reddening persisted in one female up to the 24 hour reading. Slight ocular discharge was observed in the first treated female at the 1-hour reading.
No abnormal findings were observed in the cornea or iris of any animal at any of the examinations. No corrosion was observed at any of the measuring intervals. No staining of the treated eyes by the test item was noted.
No abnormal findings were observed in the treated eye of any animal 48 hours after treatment.

Table B.6.1.5-1: Eye irritation scores of abamectin SC (A12115I) according to the Draize scheme

Time	Cornea			Iris			Conjunctiva					
							Redness			Chemosis		
Animal number	19	20	21	19	20	21	19	20	21	19	20	21
after 1 hour	0	0	0	0	0	0	1	1	1	0	1	1
after 24 hours	0	0	0	0	0	0	0	0	0	0	0	0
after 48 hours	0	0	0	0	0	0	0	0	0	0	0	0
after 72 hours	0	0	0	0	0	0	0	0	0	0	0	0
mean scores 24-72h	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
after 48 hours	0	0	0	0	0	0	0	0	0	0	0	0

CONCLUSION

The instillation of abamectin SC (A12115I) into the eye resulted in mild, early-onset and transient ocular changes. These effects were reversible and were no longer evident 48 hours after treatment.

The mean irritation scores 24 to 72 hours after application were less than the thresholds defined in Regulation (EC) 1272/2008 as amended. Therefore, according to Regulation (EC) 1272/2008 as amended, no classification is required for eye irritating properties of A12115I.

B.6.1.6 Skin sensitisation

reference	:	[redacted], 2009d	exposure	: Dermal, Week 1-3: induction, 9 exposures Day 29: challenge
Report number	:	Syngenta File No. A121151/10019	doses	: Induction: 25% Challenge: 1% and 3%
test substance		abamectin SC (A12115I)	GLP statement	: yes
species	:	Guinea Pig, Dunkin Hartley	guideline	: in accordance with OECD 406.
group size	:	20/dose 10/control	acceptability	: acceptable

STUDY DESIGN

Materials:

Test Material:	**Abamectin SC (A12115I)**
Description:	Liquid; black
Lot/Batch number:	SMU9AL002
Purity:	19.4 g/l corresponding to 1.619% w/w
CAS number:	Not available.
Stability of test compound:	Stable under storage conditions. Expiry date: 31 January 2012

Vehicle:	Purified water

Test Animals:	
Species:	Guinea pig
Strain:	Albino Dunkin Hartley Guinea Pig, CRL:(HA), SPF
Age/weight at dosing:	5-6 weeks / Test and control animals: 358 - 388 g, animals used for irritation screen: 309 - 371 g
Source:	[redacted]
Housing:	Individually in Makrolon type-4 cages with standard softwood bedding ("Lignocel", Schill AG, 4132 Muttenz/Switzerland).

Methods:

In-life dates: 13 May 2009 - 24 June 2009

Animal assignment and treatment: The "Buehler Test" modified by Ritz, H.L. and Buehler, E.V. (1980) was used. Twenty male animals (albino Dunkin Hartley guinea pigs) of the test group were treated topically with abamectin SC (A12115I) three times a week for a 3-week induction phase. Ten days after the final induction application the animals were challenged. The concentrations for the induction and the challenge were selected based on the results of two irritation screens.

Induction: The fur was clipped from the left shoulder of each test animal and the patches applied on 9 occasions over a total period of 3 weeks. Each animal received three patches per week with the test item at 25% in purified water which remained in place for approximately 6 hours each. Repeated applications were made to the same application site.
The control animals were treated in the same way with the vehicle (purified water) only and also covered occlusively.
After the last induction exposure the animals were left untreated for 9 days.
The skin responses were graded approximately 24 hours after the patches have been removed.

Challenge: The animals previously exposed during the induction period (i.e. test group) as well as the previously only with the vehicle treated control animals were challenged 10 days after the last induction exposure using the test item at 3% and 1% in purified water. The exposure period was 6 hours on a naive skin site.
The skin responses were graded approximately 24 and 48 hours after the patches had been removed.

RESULTS
Mortality / Clinical observations: There were no deaths during the course of the study, hence no necropsies were performed. No signs of systemic toxicity were observed in the animals.

Induction reactions and duration: Skin effects in all test animals during the induction phase could not be evaluated due to dark brown staining produced by the test item. No skin effect was observed in the control animals treated with purified water only during the induction phase.

Challenge reactions and duration: At the challenge discrete/patchy erythema was observed at the 24-hour reading in one control animal treated at 3% and in one test animal treated at 3% and 1% of abamectin SC (A12115I) in purified water.

Bodyweights: There were no treatment-related effects on bodyweight during the study.

Table B.6.1.6-1: Buehler test: Number of animals with positive signs of allergic skin reactions following challenge

	Test flank			
	Challenge at 3%		Challenge at 1%	
Scored after:	24 hours	48 hours	24 hours	48 hours
Main test – test group	1/20	0/20	1/20	0/20
Main test – negative vehicle control	1/10	0/10	0/10	0/10

Conclusion

Based on the results of this study, abamectin SC (A12115I) is considered not to be a skin sensitizer in the guinea pig.

According to Regulation (EC) 1272/2008 as amended, no classification is required for skin sensitisation properties of A12115I.

B.6.1.7 Supplementary studies for the combination of plant protection products

This product does not contain recommendations for combinations of plant protection products therefore supplementary studies are not required.

B.6.2 Dermal absorption

No specific data on dermal absorption are available for A12115I. Therefore it is proposed to use a default value of 10% for both concentrate and dilution, based on the physicochemical properties of abamectin (MW=867, log P_{ow}= 4.4). This is in accordance with the EFSA guidance on dermal absorption[1] which proposes the 10% default value for substances with a MW >500 and a log P_{ow} >4. The use of this default value is likely to be conservative, being significantly higher than the EU agreed value for a similar strength abamectin EC formulation (Table B.6.14.1-1).

The percentage absorptions used in the operator exposure assessment are in Table B.6. 2-1.

Table B.6.2-1: Dermal absorption end-points for the risk assessment of abamectin

End-Point	Abamectin
Dermal penetration	Concentrate: 10%
	Spray dilutions: 10%

B.6.3 Available toxicological data relating to co-formulants

CONFIDENTIAL information - data provided in Volume 4

B.6.4 Exposure data

Product information

Product: A12115I

Purpose: nematocide

Active substance (a.s.): abamectin

Product type: SC

Package size: various container sizes

Table 6.4-1 describes the critical use patterns that has been defined following of the individual GAPs for each crop.

Table 6.4-1 Summary of critical use (i.e. worst case)

Application equipment	Representative Crop	Max Application rate (kg product/ha)	Max Application rate (kg a.s./ha)	Minimum Spray dilution (L/ha)	Number applications
Greenhouse, soil drip	Pepper, aubergine, tomato, cucurbits, green beans.	**5 (L/ha)**	**0.1**	**10,000-20,000**	**4-6**

B.6.4.1 Operator exposure

Table B.6.4.1-1: Toxicological endpoints of abamectin required for evaluation of operator, worker, bystander and residential risk

Endpoint	EU agreed endpoint (Commission Implementing Regulation (EU) No. 540/2011 of 25 May 2011)	Dermal Absorption for A121151I
AOEL (mg/kg bw/day)	0.0025	
Dermal absorption of concentrate	1% (18 g/L EC)	10%
Dermal absorption of in-use dilution	1% (18 g/L EC)	10%

Estimations of potential operator exposure for the formulation A12115I are made for the intended critical uses described in table 6.4-1 and the following predictive models:

- Uniform Principles for Safeguarding the Health of Applicators of Plant Protection Products (Uniform Principles for Operator Protection);, Mitteilungen aus der Biologischen Bundesanstalt, Heft 277, Berlin 1992 (“German model”)

[1] EFSA Scientific Opinion: Guidance on Dermal Absorption (2012). EFSA Journal 10 (4): 2665

B.6.4.1.1 Estimation of operator exposure without personal protective equipment

The input parameters that were applied in the models for the operator exposure estimation are described in Table B.6. 4.1.1-1.

Table B.6. 4.1.1-1 Input parameter in the German model

Application method	Input parameter
Hand-held application, high crops	Treated area: 1 ha/day Max. dose rate: 0.1 kg abamectin/ha Operator body weight: 70 kg

The formulation is a suspension concentrate (SC) packaged in various container sizes. The estimation of potential operator exposure has been undertaken for abamectin using the critical uses (Table B.6.14.1) and the German model.

As the method of application is by soil drip and not a foliar spray, then there will not be any exposure to the operator during the application. The only point where exposure is a possibility is during mixing and loading of the tank supplying the diluted material. In some circumstances the concentrate is likely be metered directly into the irrigation water directly from the container. Below is an exposure assessment where a measure of concentrate is poured directly into a large tank of water connected to the drip system for 1 hectare of crop. The estimations were compared to EU agreed AOEL for abamectin. The operator exposure estimates assuming that no protective clothing is worn are summarized in Table B.6.4.1.1-2. The detailed calculator spreadsheet are included in Appendix 1.

Table B.6.4.1.1-2 Exposure prediction and risk assessment without PPE

Application method	**Model**	**Total systemic exposure (mg/kg bw/day)[1]**	**% of AOEL**
Hand-held application, high crops	German model	0.00034371	13.75

[1] Systemic exposure based on dermal absorption of 10%, and respiratory absorption of 100% for the concentrate during mixing and loading of A12115I.

Conclusion

The German model estimate shows that for the intended use of the formulation A12115I the predicted systemic exposure for the unprotected operator is 13.75% of the AOEL in the German model. Therefore, it is concluded according to the model calculations, that the risk for the operator mixing A12115I for use in soil drip systems on protected vegetables is acceptable without the use of personal protective equipment.

B.6.4.1.2 Estimation of operator exposure with personal protective equipment

Not required since model calculations predict the systemic exposure to abamectin to be within the AOEL without protective equipment.

B.6.4.2 Bystander and resident exposure

Bystander and residential exposure to A12115I has not been evaluated as part of an EU review for proposed critical use rate/crop. Therefore all relevant data and risk assessments are provided here and are considered adequate.

Bystander and residential exposure is generally due to drift during spray applications. This product is applied directly to the soil by drip irrigation and so no spray drift is produced. This product is also used in a controlled indoor environment and management measures exist to ensure that there is no access to bystanders or residents living nearby.

It is concluded that there is no risk of residential exposure or to the bystander as there is no likelihood of incidental short-term exposure to A12115I.

B.6.4.3 Worker exposure

Worker exposure to A12115I has not been evaluated as part of an EU review for proposed critical use rate/crop. Therefore all relevant data and risk assessments are provided and are considered adequate.

This product is applied by an irrigation soil drip system and not by foliar spray. There will be no residue on the leaf surface and therefore there is no worker re-entry exposure scenario.

It is concluded that there is no risk anticipated for the worker when re-entering crops treated with A12115I by soil drip irrigation.

B.6.5 Exposure and risk assessment

Conclusions on risk assessments for operators, bystanders and workers

Operator

Using the German model, a safe use was identified for operators, without PPE, for soil drip irrigation on pepper, aubergine, tomato, cucurbits, green beans in greenhouses

Bystander and residents

Safe uses for bystanders and residents were identified as there is no likelihood of incidental short-term exposure to A12115I.

Worker

Safe uses for workers without PPE were identified as there be no residue on the leaf surface.

B.6.6 References relied on

Literature search

A literature search was carried out by the notifier on 3/12/2013. The search method is considered acceptable by the RMS.

Databases:

MEDLINE
EMBASE
EMBAL
ESBIOBASE
AGRICOLA
BIOSIS
CABA
CAPLUS
FSTA
FROSTI
GEOREF
TOXCENTER
PQSCITECH
PASCAL
SCISEARCH
ANABST

Search Limitation:
Searches were limited to 2004 onwards.

Search strategy for substances:
All databases listed above were searched for CAS Registry Number, IUPAC and common name as listed in Section 2.

Overview of the search process
Each database was searched separately for the entire set of search terms detailed in the sections below. Duplicates entries were removed from each database search. For the initial rapid assessment, study titles and/or abstracts were scanned to identify the potential relevance of studies for each section. Studies dismissed immediately included those clearly not related to each section and those unambiguously belonging to other sections. A list of potentially relevant references following this initial rapid assessment is presented.

Search results
Search results are presented below in the following five sections. The searches were conducted on the 3rd December 2013. These were searched for appropriate references for toxicology, dietary, environmental, ecotoxicology and product chemistry.

Search for Toxicological and Toxicokinetic studies

The following search terms were used in addition to the compound and metabolite names, synonymns and CAS numbers detailed in section 2 plus (nematicide or nematocide or (nematode control)):

L1 QUE (MUTAG? OR CANCER? OR TERATO? OR GENETOX? OR CARCIN?)
L2 QUE (TUMOUR? OR TUMOR? OR CYTOTOX? OR GENOTOX? OR MELANOM?)
L3 QUE (NEUROTOXI? OR LD50 OR IC50 OR ((LD OR IC)(W)50))
L4 QUE (((LONG OR SHORT)(W)TERM?)(L)(EFFECT? OR STUD? OR TOXIC?))
L5 QUE (ENDOCRIN? OR INHALAT? OR IRRITAT? OR REPROTOX?)
L6 QUE (PERCUTANEOU? OR DERMAL? OR ORAL? OR INTOXICAT? OR INGEST?)
L7 QUE (((REPRODUCT? OR EMBRYO? OR FOET? OR DEVELOP?)(5A)TOXI?))
L8 QUE ((ACUTE? OR CHRONIC?)(5A)(EFFECT? OR TOXIC? OR TOXIN#))
L9 QUE (GIRL# OR CHILD OR CHILDREN OR PATIENT# OR HUMAN# OR MAN)
L10 QUE (MEN OR WOM!N OR BOY# OR WORKER# OR OPERATOR# OR FARMER#)
L11 QUE (APPLICATOR# OR PERSONNEL? OR WORKFORCE OR EMPLOYEE#)
L12 QUE (MAMMAL? OR RODENT# OR RAT OR RATS OR MOUSE OR MICE)
L13 QUE (ACCIDENT? OR POISON? OR ALLERG? OR EXPOSURE? OR EXPOSE#)
L14 QUE (OCCUPAT? OR EPIDEMIOL? OR SENSITIZ? OR SENSITIS?)
L15 QUE ((HEALTH OR ADVERSE)(5A)(EFFECT# OR RISK#))
L16 QUE (MEDICAL OR (FIRST(W)AID) OR (TOXIC?(3A)STUD?) OR THERAPE?)
L17 QUE (TOXICOKINETIC# OR EXTRACTAB? OR (RADIO(W)LABEL?))
L18 QUE (DOG# OR (GUINEA(W)PIG#) OR RABBIT# OR SKIN? OR EYE#)
L19 QUE (HAND# OR DERMAL? OR BYSTANDER# OR RESIDENT#)
L20 QUE ((ROTAT? OR SUCCEDING OR FOLLOWING)(3A)CROP#)
L21 QUE ((DIETARY OR CONSUM? OR CUMULAT? OR AGGREGAT?)(5A)RISK?)
L22 QUE (L1 OR L2 OR L3 OR L4 OR L5 OR L6 OR L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21)

Reporting/Overview of the search process for Toxicological and Toxicokinetic studies

Data requirement(s) captured in the search	**Number (2004-2013)**
Total number of *summary records* retrieved after *all** searches of peer-reviewed literature (excluding duplicates)	60
Number of *summary records* excluded from the search results after rapid assessment of title and/or abstract for relevance	58

*both from bibliographic databases and other sources of peer-reviewed literature

A list of potentially relevant references following initial rapid assessment of titles and/or absracts is given below.

Toxicological and Toxicokinetic references

Authors	Title	Source
Castanha Zanoli Juliana C; Maioli Marcos A; Medeiros Hyllana C D; Mingatto; Fabio E	Abamectin affects the bioenergetics of liver mitochondria: A potential mechanism of hepatotoxicity.	Toxicology in vitro: an international journal published in association with BIBRA, (2012 Feb) Vol. 26, No. 1, pp. 51-6. Electronic Publication. Date: 17 Oct 2011. Journal code: 8712158. E-ISSN: 1879-3177. L-ISSN: 0887-2333.
Bartram, D. J.; Noe, L.; Krautmann, M. J.; Lane, S.; Geurden, T.	Clinical safety of rapid sequential administration of moxidectin injection and oral derquantel-abamectin as a quarantine treatment for introduced sheep.	Veterinary Record (2013), Volume 172, Number 16, 426 p. ISSN: 0042-4900

Reference list

Data point	Author(s)	Year	Title Company Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Data protection claimed Y/N	Justification if data protection is claimed	Owner
KIIIA1 7.1.1 / 01	[redacted]	2009a	Abamectin SC (A12115I) - Acute Oral Toxicity Study in the Rat (Up and Down Procedure) Syngenta - Jealott's Hill, Bracknell, United Kingdom [redacted] GLP, not published Syngenta File No A12115I_10020	Y	Y	Y	SYN
KIIIA1 7.1.2 / 01	[redacted]	2010	Abamectin SC(A12115I) - Acute Toxicity Study in Rats Syngenta - Jealott's Hill, Bracknell, United Kingdom [redacted] GLP, not published Syngenta File No A12115I_10021	Y	Y	Y	SYN
KIIIA1 7.1.3 / 01	[redacted]	2009	Abamectin SC (A12115I) - Acute 4 Hour (Nose Only) Inhalation Study In The Rat Syngenta - Jealott's Hill, Bracknell, United Kingdom [redacted],	Y	Y	Y	SYN

			[redacted] GLP, not published Syngenta File No A12115I_10011				
KIIIA1 7.1.4 / 01	[redacted]	2009b	Abamectin SC (A121151) - Primary Skin Irritation Study in Rabbits (4 Hour Semi-Occlusive Application) Syngenta [redacted] GLP, not published Syngenta File No A12115I_10015	Y	Y	Y	SYN
KIIIA1 7.1.5 / 01	[redacted]	2009c	Abamectin SC (A121151) - Primary Eye Irritation Study in Rabbits Syngenta [redacted] GLP, not published Syngenta File No A12115I_10016	Y	Y	Y	SYN
KIIIA1 7.1.6 / 01	[redacted]	2009d	Abamectin SC (A12115I) - Contact Hypersensitivty in Albino Guinea Pigs, Buehler Test (9-induction) Syngenta - Jealott's Hill, Bracknell, United Kingdom [redacted] GLP, not published Syngenta File No A12115I_10019	Y	Y	Y	SYN

Appendix 1: Detailed exposure models

abamed	AF =	0	systemic AOEL =	0,0025	mg/kg bw x d

= HIGH CROP TRACTOR MOUNTED =

Treated area per day	A =	1	ha/d	at BBA = 8
Use rate	R =	0,1	kg a.i./ha	

Mixing/loading of the product [mg/person per kg a.				Appl. of the spray [mg/pers. per kg a.i.]	
	liquid	solid: WP	solid: WG	l*a = 0,018	D*a/c = 1,2
l*m	0,0006	0,07	0,008	D*a/h = 0,7	D*a/b = 9,6
D*m/h	2,4	6	2		

Estimated inhalation exposure:

Im = l*m x R x A	0,0006	0,1	1	0,00006	mg/pers. x d
Ia = l*a x R x A	0	0,1	1	0	mg/pers. x d
			I, in total =	**0,00006**	**mg/pers. x d**

Estimated dermal exposure:

Dm/h = D*m/h x R x A	2,4	0,1	1	0,24	mg/pers. x d
Da/h = D*a/h x R x A	0	0,1	1	0	mg/pers. x d
Da/c = D*a/c x R x A	0	0,1	1	0	mg/pers. x d
Da/b = D*a/b x R x A	0	0,1	1	0	mg/pers. x d
			D, in total =	**0,24**	**mg/pers. x d**

Estimated inh. exp.		**PPE**	**factor**		
Im =	0,00006	-	1	0,00006	mg/pers. x d
Ia =	0	-	1	0	mg/pers. x d
				0,00006	**mg/pers. x d**

Estimated derm. exp.					
Dm/h =	0,24		1	0,24	mg/pers. x d
Da/h =	0		1	0	mg/pers. x d
Da/c =	0		1	0	mg/pers. x d
Da/b =	0		1	0	mg/pers. x d
				0,24	**mg/pers. x d**

		Estimated exposure		Systemic exposure	
	abs. rate	**without PPE**	**with PPE**	**without PPE**	**with PPE**
Inhalation: m/l	100%	0,00006	0,00006	0,00006	0,00006
Inhalation: appl.	100%	0	0	0	0
Dermal: m/l	10%	0,24	0,24	0,024	0,024
Dermal: appl.	10%	0	0	0	0
			mg/pers./d:	0,02406	0,02406
kg bw:	70		mg/kg bw/d:	0,00034371	0,00034371
syst. AOEL:	0,0025		**% of AOEL:**	**13,7485714**	**13,7485714**

Possible PPE: specific instructions	Abbr.	Red.-factor	to lower:
Particle filtering half mask (m/l)	ST 110	0,08	**Im**
Half mask with comb. filter (m/l)	ST 210	0,02	
Particle filtering half mask (appl.)	ST 120	0,08	**Ia**
Half mask with comb. filter (appl.)	ST 220	0,02	
Protective gloves (m/l)	**SS 110**	**0,01**	**Dm/h**
Protective gloves (appl.)	**SS 120**	**0,01**	**Da/h**
Half mask (appl.)	ST 120 / 220	0,8	**Da/c**
Broad-brimmed headgear (appl.: high crops)	**SS 420**	**0,5**	
Hood and visor (appl.: high crops)	SS 520	0,05	
Protective garment + sturdy footwear (appl.)	**SS 220**	**0,05**	**Da/b**