COMPETENT AUTHORITY REPORT

THIAMETHOXAM (PT 18)

Document IIIA
Active Substance

Rapporteur Member State: Spain
~~January 2009~~ April 2011

INDEX

Section A1 Applicant

Annex Point IIA1

1.1 Applicant

Syngenta European Center
GU2 7YH Guildford
United Kingdom

Contact person

[redacted]
Syngenta European Office
Priestly Road
GU2 7YH Guildford
[redacted]

1.2 **Manufacturer of Active Substance** (if different)

Syngenta Crop Protection AG
CH - 4002 Basle
Switzerland

Location of plant

[redacted]

Syngenta Crop Protection AG.

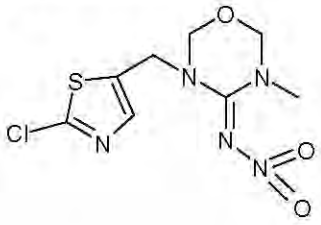
Contact point :

[redacted]

1.3 Manufacturer of Product(s) (if different)

1) Product 1

Section A2 Identity of Active Substance

Subsection (Annex Point)			Official use only
2.1	**Common name**	*thiamethoxam*	
2.2	**Chemical name**	***IUPAC nomenclature*** *:3-(2-chloro-thiazol-5-ylmethyl)-5-methyl-[1,3,5]oxadiazinan-4-ylidene-N-nitroamine* ***CA nomenclature*** *:3-[(2-chloro-5-thiazolyl)methyl]tetrahydro-5-methyl-N-nitro-4H-1,3,5-oxadiazin-4-imine*	
2.3	**Manufacturer´s development code number(s)**	*CGA 293343*	
2.4	**CAS No and EC numbers**		
2.4.1	**CAS-No**	*153719-23-4*	
2.4.2	**EC-No**	*428-650-4*	
2.4.3	**CIPAC-No**	*637*	
2.5	**Molecular and structural formula, molecular mass**		
2.5.1	**Molecular formula**	$C_8H_{10}ClN_5O_3S$	
2.5.2	**Structural formula**		
2.5.3	**Molecular mass**	*291.7*	
2.6	**Method of manufacture of the active substance (IIA2.1)**	*CONFIDENTIAL* ***information*** *- data provided separately*	
2.7	**Specification of the purity of the active substance, as appropriate**	*min. 980 g / kg*	
2.8	**Identity of impurities and additives, as appropriate**	*CONFIDENTIAL* ***information*** *- data provided separately*	
2.9	**The origin of the natural active substance or the precursor(s) of the active substance**	*Not applicable*	

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	May 2005
Materials and methods	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	[redacted]

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**	**X1**
2.10.1.1	**Production**	
	i) Description of process	
	ii) Workplace description	
	iii) Inhalation exposure	
	iv) Dermal exposure	
2.10.1.2	**Intended use(s)**	
	1. Professional Users	
	i) Description of application process	
	ii) Workplace description	
	iii) Inhalation exposure	
	iv) Dermal exposure	
	2. Non-professional Users including the general public	
	(i) via inhalational contact	
	(ii) via skin contact	
	(iii) via drinking water	
	(iv) via food	
	(v) indirect via environment	
2.10.2	**Environmental exposure towards**	

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

active substance

2.10.2.1 Production

(i) Releases into water

(ii) Releases into air

(iii) Waste disposal

2.10.2.2 Intended use(s)

Affected compartment(s):

water

sediment

air

soil

Predicted concentration in the affected compartment(s)

water

sediment

air

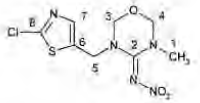
soil

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	June 2005
Comments	[redacted]

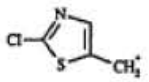
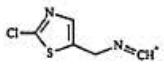
Section A3 Physical and Chemical Properties of Active Substance

Subsection (Annex Point)	Method	Purity/ Specification	Results Give also data on test pressure, temperature, pH and concentration range if necessary	Remarks/ Justification	GLP (Y/N)	Reliability	Reference	Official use only
3.1 Melting point, boiling point, relative density								
3.1.1 Melting point	EEC A.1 OECD No.102	99.7 %	139.1°C	Capillary method	Y	1	Das, 1995a	
3.1.2 Boiling point	EEC A.2 OECD No.103	99.3 %	Thermal decomposition starts at about 147 °C (i.e. before the boiling point is reached)	Differential scanning calorimetry	Y	1	Das, 1997	
3.1.3 Bulk density/ relative density								
Density	EEC A.3	99.7 %	$1.57 \cdot 10^3$ kg / m³, therefore , relative density: 1.57	Air comparison pycnometer method	Y	1	Füldner, 1995	
3.2 Vapour pressure	EEC A.4 OECD No. 104	99.7 %	temperature: 25 °C $6.6 \cdot 10^{-9}$ Pa (extrapolated)	Gas saturation method	Y	1	Geoffroy, 1995	
3.2.1 Henry´s Law Constant			calculated: $4.7 \cdot 10^{-10}$ Pa · m³ / mol at 25°C	water solubility at 25 °C : 4100 g/m³ vapour pressure at 25 °C: $6.6 \cdot 10^{-9}$ Pa			Burkhard, 1996	
3.3 Appearance								
3.3.1 Physical state	visual test	pure a.i. (99.7 %)	fine crystalline powder		Y	1	Das, 1995b	
		technical grade a.i (98.2 %)	fine powder		Y	1	Das, 1998	
3.3.2 Colour	visual test	pure a.i. (99.7 %)	slightly cream		Y	1	Das, 1995b	
		technical grade a.i (98.2 %)	off-white		Y	1	Das, 1998	
3.3.3 Odour	organoleptic test	pure a.i. (99.7 %)	odourless		Y	1	Das, 1995b	
		technical grade a.i (98.2 %)	odourless		Y	1	Das, 1998	
3.4 Absorption spectra								

Section A3 Physical and Chemical Properties of Active Substance

Subsection (Annex Point)	Method	Purity/ Specification	Results Give also data on test pressure, temperature, pH and concentration range if necessary	Remarks/ Justification	GLP (Y/N)	Reliability	Reference	Official use only
UV/VIS	SOP 201/2	99.7 %	For the absorption maxima at 255 nm the molar extinction coefficient was determined to be 16800 l / mol · cm in neutral solution. No absorption maximum between 290 nm and 750 nm was observed. Only slightly variations on extinction coefficients were observed at different pH.	Concentration and solvent: 2.2 mg in 100 ml methanol Quartz cell : 10 mm pathlength Reference solvent :methanol	Y	1	Birk, 1995	
IR	SOP 202/2	99.7 %	Characteristic bands: 1598 cm^{-1} (NO2 stretch assym. And C=N- stretch sym.) 1265 cm^{-1} (NO2 stretch)	Sample preparation : KBr pellet (1 mg test substance in 300 mg KBr)	Y	1	Birk, 1995	
NMR	^{1}H-~~RMN~~NMR: SOP 214/1	99.7 %	7.54 (s, 1H); 5.02 (s, 2H); 4.94 (s, 2H); 4.74 (s, 2H); 2.82 (s, 3H)	Operating temperature : room temperature Solvent :Acetone d6 Nucleus :^{1}H (300 MHz) I.S.: Acetone d6	Y	1	Birk, 1995	
	^{13}C-~~RMN~~NMR:	99.3 %	 Shift (ppm) Assignment 35 1 44 5 80 3, 4	Operating temp : 293 K Solvent : CDCl3 Nucleus :^{13}C (75 MHz) I.S.:TMS	Y	1	Birk, 1998	

Section A3 Physical and Chemical Properties of Active Substance

Subsection (Annex Point)	Method	Purity/ Specification	Results Give also data on test pressure, temperature, pH and concentration range if necessary	Remarks/ Justification	GLP (Y/N)	Reliability	Reference	Official use only
			134 6 141 7 154 8 157 2					
MS	SOP 204/2	99.7 %	m / z 291 M+ (not detected) 247 M+ - CH_2OCH_2 245 M+ - NO_2 215 m/z 245 – CH_2O 209 m/z 245 – HCl 179 m/z 209 – CH_2O  159  132	Type of analyzer : quadrupole Ionization mode : electron impact Detection : scan mode Ionizing energy : 70 eV	Y	1	Birk, 1995	
3.5 Solubility in water *including effects of pH (5-9)*								
Water solubility	EEC A.6 OECD No. 105	99.7 %	result: 4100 mg/l temperature: 25 °C	Flask method	Y	1	Stulz, 1995a	
3.6 Dissociation constant (-)	OECD 112	99.7 %	The test substance has no dissociation within the range pH 2 to pH 12		Y	1	Stulz, 1995b	
3.7 Solubility in organic solvents, including the effect of temperature on	SOP 209/5	98.2 %	temperature: 25 °C n-hexane: < 1 mg/l toluene: 680 mg/l dichloromethane: 110 g/l		Y	1	Stulz, 1998	

Section A3 Physical and Chemical Properties of Active Substance

Subsection (Annex Point)	Method	Purity/ Specification	Results Give also data on test pressure, temperature, pH and concentration range if necessary	Remarks/ Justification	GLP (Y/N)	Reliability	Reference	Official use only
solubility			methanol: 13 g/l n-octanol: 620 mg/l acetone: 48 g/l ethyl acetate: 7 g/l					
3.8 Stability in organic solvents used in b.p. and identity of relevant breakdown products								**X1**
3.9 Partition coefficient n-octanol/water log Pow	*including effects of pH (5-9)* EEC A.8 OECD No. 107	99.7 %	result: -0.13 temperature: 25 °C pH: 6.84	Shake-flask method	Y	1	Stulz, 1995c	
3.10 Thermal stability, identity of relevant breakdown products	OECD No. 113	98.2 %	The sample shows neither without nor with air any peak between room temperature and melting point of the substance, resp. 150 °C.		Y	1	Angly, 1998a	
3.11 Flammability, including auto-flammability and identity of combustion products	EEC A.10 (Flammability of solids) EEC A.16 (Relative self-ignition temperature for solids)	98.2 % 98.2 %	The substance is not considered highly flammable No self-ignition was observed		Y Y	1 1	Angly, 1998b Angly, 1998c	
3.12 Flash-point	Not required as the test substance is a solid with a melting point > 40 °C					1		

Section A3 Physical and Chemical Properties of Active Substance

Subsection (Annex Point)	Method	Purity/ Specification	Results Give also data on test pressure, temperature, pH and concentration range if necessary	Remarks/ Justification	GLP (Y/N)	Reliability	Reference	Official use only
3.13 Surface tension	OECD No.115	98.2 %	result: 71.7 mN/m temperature: 20 °C	Wilhelmy plate method	Y	1	Hörmann, 1998	
3.14 Viscosity	Not required as the test substance is a solid							
3.15 Explosive properties	EEC A.14	98.2 %	The substance is not considered an explosive, as concluded from test results on: Thermal sensitivity: effect of a flame Mechanical sensitivity: shock and friction		Y	1	Angly, 1998d	
3.16 Oxidizing properties	EEC A.17	98.2 %	The substance is not considered an oxidizing substance		Y	1	Angly, 1998e	
3.17 Reactivity towards container material								**X2**

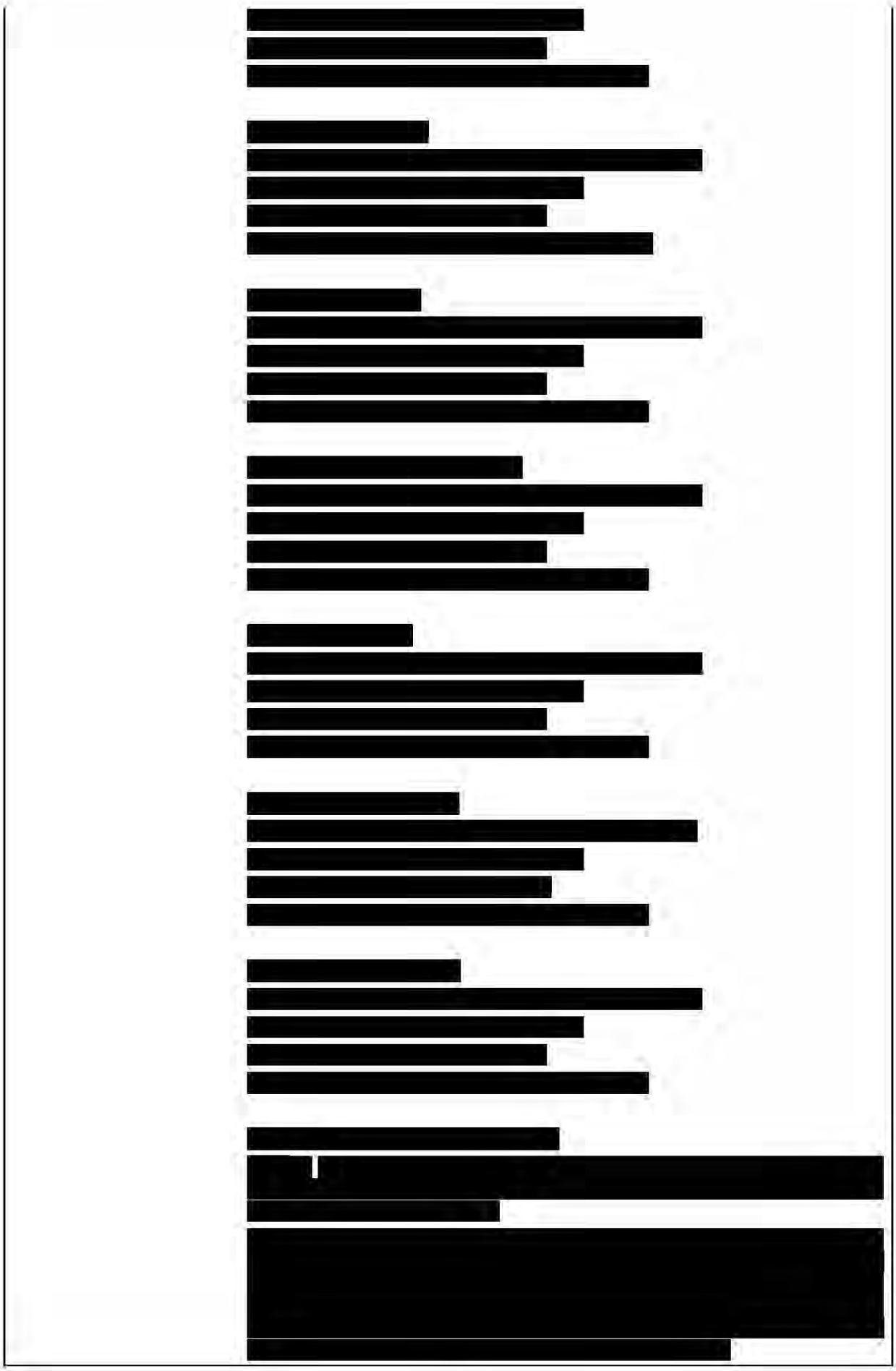
Evaluation by Competent Authorities

EVALUATION BY RAPPORTEUR MEMBER STATE

Date May 2005

Comment

Evaluation of data submitted under section A3



Section A4.1	Analytical Methods for Detection and Identification Active substance

	Evaluation by Competent Authorities
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	June 2005
Comments	[redacted]

			Official use only
		1 REFERENCE	
1.1	**Reference**	Dull, B (2003a) Determination of content by HPLC SA-1/1, 21.02.2003 not GLP, not published Syngenta File N° CGA293343/1694 Dull, B (2003b) Validation of analytical method SA-1/1 110033, 24.03.2003 GLP, not published Syngenta File N° CGA293343/1709	
1.2	**Data protection**	Yes/	
1.2.1	**Data owner**	Syngenta Crop Protection AG	
1.2.2	**Companies with letter of access**		
1.2.3	**Criteria for data protection**	[redacted]	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**		
2.2	**GLP**	Yes	
2.3	**Deviations**	None	
		3 MATERIALS AND METHODS	
3.1	**Preliminary treatment**		
3.1.1	**Enrichment**	The technical material is dissolved in 0.1% aqueous phosphoric acid/ acetonitrile (8+2)	
3.1.2	**Cleanup**	No purification steps are necessary	
3.2	**Detection**		
3.2.1	**Separation method**	HPLC chromatography on a Nucleodur C18 column using 0.1 % phosphoric acid in water / acetonitrile / methanol (80 / 5 / 15) as eluent with a linear gradient program	
3.2.2	**Detector**	UV detector, 254 nm	
3.2.3	**Standard(s)**	External standard.	
3.2.4	**Interfering substance(s)**	There are no substances which would interfere with the detection of the analyte	
3.3	**Linearity**		
3.3.1	**Calibration range**	50-150% of weight of active substance	

3.3.2	**Number of measurements**	5 data points
3.3.3	**Linearity**	$r^2 = 0.9996$
3.4	**Specifity: interfering substances**	The HPLC method is able to separate the active substance thiamethoxam from its by-products and the solvent
3.5	**Recovery rates at different levels**	98.0 – 100.4 % Mean: 99.5%
3.5.1	**Relative standard deviation**	1.3 %
3.6	**Limit of determination**	
3.7	**Precision**	
3.7.1	**Repeatability**	Relative standard deviation : 0.21% Mean value of repeatability stuy: 99.26 %
3.7.2	**Independent laboratory validation**	

98/8 Doc IIIA section No.	**4.2 / 01 &02**	**Analytical methods including recovery rates and the limits of determination for the active substance, and for residues thereof, and where relevant in/on the following: (a) Soil**
91/414 Annex Point addressed	**II 4.2.2 / 01 & 03 & 05**	**Analytical methods for determination of residues – residues in soil**

Title of the Study	**Determination of CGA 293343 and CGA 322704 by HPLC, plant material, soil (including validation)**
Dossier Reference:	4.2.2 (4.2.1/05), 4.2.2 (4.2.1/03, validation)
Method Numbers: Author: Novartis file number:	REM 179.03 P. Mair (analytical method), C. Giannone (validation) 293343 – 206, 293343 – 514 (validation)
Name and address of the testing facility:	Ciba-Geigy Ltd, Basel, Switzerland
Test Substance:	CGA 293343
Date of Issue:	May 5, 1998, July 21, 1998 (validation)
Compliance with GLP:	Yes [X] No, but complies with sound scientific principles [ ]
Reliability indicator	1

Findings

Method: For quantification of thiamethoxam and CGA 322704 in soil (25 g, dry matter content), samples are extracted by shaking with water / methanol (10 ml, 1 + 1; vol. + vol.) for 1h at 260 r.p.m. An aliquot of the filtered extract is concentrated to 7 ml and diluted with water and passed through a phenyl solid-phase cartridge. The analyte is eluted from the phenyl cartridge with water / methanol (1+ 1; vol. + vol.). The volume of the eluate is reduced to 1.5 ml by evaporating under 3 ml reduced pressure. After diluting the concentrated eluate with water to 2.5 ml, this solution is injected into a HPLC two column switching system with UV-detector (Column 1: 125 mm x 2 mm Nucleosil C18 5 µm and Column 2: 125 mm x 2 mm Nucleosil 100 Phenyl 7µm, 255 nm or 270 nm for CGA 293343 and for CGA 322704 respectively. Mobile phase 1: water/methanol (85:15) and Mobile phase 2: water/acetonitrile (8:2).

Specificity: No interference was detected during method validation. A confirmatory method using HPLC/MS/MS is proposed.

Linearity: calibration curve is provided as part of method validation.

Accuracy: The accuracy of the method is established based on the findings for specificity, recovery and linearity. Recovery > 70 %. LOQ = 0.002 ppm. See Table 1.

Repeatability: cv % < 20 %. See Table 1.

Table 1

Validation of Rem 179.03						
Reference analyte	**matrix**	**Fortification level [mg/kg]**	**Recovery rate [%]**		**cv [%]**	**n**
			mean	**range**		
thiamethoxam	soil	0.002	99	95 - 106	6	3
		0.02	77	64 - 94	20	3
CGA 322704	soil	0.002	101	94 - 106	6	3
		0.02	78	66 - 95	19	3

Conclusions: LOQ of 0.002 mg a.i. / kg soil

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	June 2005
Materials and methods	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	[redacted]

98/8 Doc IIIA section No.	**4.2 / 03 & 04**	**Analytical methods including recovery rates and the limits of determination for the active substance, and for residues thereof, and where relevant in/on the following: (b) Air**
91/414 Annex II Point addressed	**II 4.2.4 / 01 & 02**	**Analytical methods for determination of residues – residues in air**

Title of the Study	**Determination of CGA 293343 by high performance liquid chromatography (including validation)**
Dossier Reference:	4.2.4/01, 4.2.4/02 (validation)
Method number: Author: Novartis File No.:	REM 179.04 R.Tribolet (analytical method), R. Tribolet (validation) 293343 – 343, 293343 – 344 (validation)
Name and address of the testing facility:	Novartis Crop Protection AG, Basel, Switzerland
Test substance:	CGA 293343
Date of issue:	October 20, 1997, October 20, 1997 (validation)
Compliance with GLP:	Yes [X] No, but complies with sound scientific principles [ ]
Reliability indicator	1

Findings

Method: Thiamethoxam is sorbed from air in XAD-2 sorbent tubes. Air sampled for 6h at a flow rate of 0.5 L/min. The different layers of an air sampling tube are separated and thiamethoxam is extracted with methanol (2 x 5 ml) using an ultra sonic bath (2 x 5 min). The methanol is evaporated and the residue is dissolved in 5 ml methanol / water (3 + 7; vol. + vol.). Quantitation of thiamethoxam is done by HPLC using UV detection (Column Spherisorb PC 18, 5 µm, UV 255 nm. Mobile phase: methanol water (3 +7; vol + vol).

Specificity: No interferences were observed.

Linearity: : The accuracy of the method is established based on the findings for specificity, recovery and linearity. Validation curve provided as part of the method calibration.

Accuracy: Mean recovery 90 % at LOQ.

Repeatability: cv % = 3 at LOQ.

Reference (analyte)	matrix	Fortification level [µg/m^3]	Recovery rate [%]		cv [%]	n
			mean	range		
(thiamethoxam)	air	0.5	90	84 - 93	3	8
		20	87	83 - 89	2	8

Reproducibility: not tested since there is not clean-up step within the method.

Conclusions: LOQ = 0.5 **µg/m^3**

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	June 2005
Materials and methods	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	[redacted]

98/8 Doc IIIA section No.	**4.2 / 05 & 06 & 07**	**Analytical methods including recovery rates and the limits of determination for the active substance, and for residues thereof, and where relevant in/on the following: (c) Water**
91/414 Annex Point addressed	**II 4.2.3 / 01 & 02 & 03**	**Analytical methods for determination of residues – residues in water**

Title of the Study	**Determination of CGA 293343 and CGA 322704 by HPLC, potable water (including validation)**
Dossier Reference:	4.2.3/01, 4.2.3/02 (validation), 4.2.3/03 (validation surface water)
Method Number: Author: Novartis file No.:	REM 179.05 P. Mair (analytical method), P. Mair (validation), P. Mair (validation surface water) 293343 – 389, 293343 – 390 (validation), 293343 – 697 (validation suface water)
Name and address of the testing facility:	Novartis Crop Protection AG, Basel, Switzerland
Test substance:	CGA 293343
Date of issue:	December 2, 1997 (analytical method) December 16, 1997 (validation) September 11, 1998 (validation surface water)
Compliance with GLP:	Yes [X] No, but complies with sound scientific principles [ ]
Reliability indicator	1

Method: Samples of potable water (200 ml) are extracted by solid phase extraction on a Lichrolut EN solid-phase extraction cartridge. The disk is washed with water/ methanol (3 ml; 1 + 1; vol. + vol.). The analytes are eluted with acetonitrile-methanol (5 ml; 2 + 8; vol. + vol.). The volume of the eluate is reduced to less than 0.5 ml by evaporating under reduced pressure. The concentrated eluate is diluted with water (2 ml).

For surface water samples an additional cleanup step using a phenyl cartridge is necessary. The surface water 20 ml is passed through the cartridge and the eluate is discarded. The cartridge is mounted on top of the EN cartridge. The analytes are eluted with 3 ml of water / methanol (1 + 1; vol. + vol.) from the phenyl onto the EN cartridge. The eluate and the phenyl cartridge are discarded. Further cleanup is done as described above for the potable water samples excluding the wash step for the EN cartridge. Final quantitation of thiamethoxam and CGA 322704 is performed by HPLC using UV detection. (Column 125 mm x 2 mm Nucleosil C18-5µm. Mobile phase: water-acetonitrile (85 + 15; vol + vol) at 0.25 ml/min. In case of problems, it is possible to use the 2 system approach.

Specificity: No interferences are detected. Two confirmatory HPLC/MS/MS methods are provided.

Linearity: Validation curve provided as part of the method calibration.

Accuracy: The accuracy of the method is established based on the findings for specificity, recovery and linearity. Recovery > 90 %.

Repeatability: cv % < 20 %.

Reference (analyte)	matrix	Fortification level [µg/L]	Recovery rate [%]		cv [%]	n
			mean	Range		
Mair, 1997b (IIA, 4.2.3/02)						
(thiamethoxam)	water	0.05	102	71 - 113	14	11*
		0.50	87	79 - 92	5	8
(CGA 322704)	water	0.05	94	86 - 105	7	11*
		0.50	90	82 - 95	5	8
Mair, 1998 (IIA, 4.2.3/03)						
(thiamethoxam)	surface water (River Rhein)	0.5	109	100 - 114	5	8
		5.0	95	87 - 105	7	8
(CGA 322704)	surface water (River Rhein)	0.5	95	85 - 102	7	8
		5.0	96	90 - 103	5	8
(thiamethoxam)	surface water (River Birs)	0.5	84	78 - 92	8	8
(CGA 322704)	surface water (River Birs)	0.5	90	87 - 99	6	8

Conclusions: LOQ (drinking water) = 0.05 µg/L; LOQ (surface water) = 0.5 µg/L

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	June 2005
Materials and methods	[redacted]
Conclusion	[redacted]d.
Reliability	[redacted]
Acceptability	[redacted].
Remarks	[redacted]

* including results of independent lab validation

98/8 Doc IIIA section No.	**4.2 / 08 & 09**	**Analytical methods including recovery rates and the limits of determination for the active substance, and for residues thereof, and where relevant in/on the following: (d) Animal and human body fluids and tissues**
91/414 Annex Point addressed	**II 4.2.1 / 01 & 02**	**Analytical methods for determination of residues – residues in and/or on plants, plant products, foodstuffs (of plant and animal origin), feeding stuffs**

Title of the Study	**Analytical method for the determination of residues of CGA 293343 and the metabolite CGA 322704 in animal and crop substrates by high performance liquid chromatography with detection by UV and mass spectrometry, including validation data (including independent laboratory validation)**
Dossier Reference:	4.2.1/01 , 4.2.1 /02
Method Numbers: Author: Novartis file number:	AG-675 [redacted] 293343 – 820, 293343 – 847 (validation)
Name and address of the testing facility:	[redacted]
Test Substance:	CGA 293343
Date of Issue:	September 18, 1998, November 11, 1998 (validation)
Compliance with GLP:	Yes [X] No, but complies with sound scientific principles [ ]
Reliability indicator	1

Findings

Method: Ten-gram samples are extracted twice by homogenisation in acetonitrile / water (8 + 2, vol. + vol.). Liquid samples such as milk and eggs, are extracted by shaking for 20 minutes in acetonitrile / water (8 + 2, vol. + vol.). The total extract volume is 200 mL.

A 100 mL aliquot is measured (for milk the entire 200 mL is analysed). A liquid-liquid partition using toluene and hexane is performed prior to evaporation. The reduced, aqueous sample is first purified by reverse-phase solid-phase extraction (SPE) by loading onto a phenyl cartridge. After elution from the phenyl SPE cartridge with methanol / water (1 + 1; vol. + vol.), the sample is evaporated to aqueous and the compounds are partitioned into ethyl acetate. The ethyl acetate fraction is evaporated and the sample is further purified by normal phase SPE using both an amino cartridge and an alumina cartridge. After elution from the alumina column, the samples are evaporated and reconstituted in mobile phase for determination by normal phase HPLC/UV. The normal phase column is a Waters Spherisorb S5 NH_2 (250 mm x 4.6 mm I.D.), with a mobile phase of hexane:ethyl acetate: isopropanol:methanol (11 + 3 + 1 + 1; vol. + vol. + vol. + vol.).

Specificity: The method is specific and confirmation is possible by evaporating the final fraction, reconstituting the sample in CH_3CN :water and analysing using HPLC/MS or HPLC/MS/MS. No interferences were detected during the validation study, however in residue trials minor interferences were detected in broccoli and cabbage. Reanalysis with HPLC/MS solved the problem.

Linearity: Calibration plots gave a correlation coefficient > 0.99 (number calibration points = 6).

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

Repeatability: See table below

Reference (analyte)	Matrix	Fortification level [mg/kg]	Recovery rate [%]		cv [%]	n
(thiamethoxam)	fat (cow, omental)	0.01	--	80 / 86	--	2
		0.2	--	83	--	1
		2.0	--	86 /79	--	2
(CGA 322704)	fat (cow, omental)	0.01	--	85 /87	--	2
		0.2	--	87	--	1
		2.0	--	90 / 85	--	2
(thiamethoxam)	kidney (cow)	0.01	--	88 / 91	--	2
		0.1	--	83	--	1
		1.0	--	83	--	1
(CGA 322704)	kidney (cow)	0.01	--	90 / 94	--	2
		0.1	--	87	--	1
		0.5	--	90 / 85	--	1
(thiamethoxam)	liver (cow)	0.01	--	85 / 84	--	2
		0.1	--	86	--	1
		0.5	--	90 / 85	--	2
(CGA 322704)	liver (cow)	0.01	--	92 / 91	--	2
		0.1	--	88	--	1
		0.5	--	90 / 86	--	2
(thiamethoxam)	meat (goat muscle)	0.01	--	86 / 86	--	2
		1.0	--	88	--	1
(CGA 322704)	meat (goat muscle)	0.01	--	88 / 88	--	2
		1.0	--	89	--	1
(thiamethoxam)	Milk (goat)	0.005	--	113 / 104	--	2
		0.5	--	88	--	1
(CGA 322704)	Milk (goat)	0.005	--	96 / 96	--	2
		0.5	--	90	--	1
(thiamethoxam)	Eggs	0.01	--	92	--	1
		0.2	--	81	--	1
		2.0	--	83 / 84	--	2
(CGA 322704)	Eggs	0.01	--	95	--	1
		0.2	--	85	--	1
		2.0	--	88 / 89	--	2
(thiamethoxam)	fat (poultry)	0.01	--	98 / 85	--	2
		0.1	--	90	--	1
		1.0	--	83 / 86	--	2
(CGA 322704)	fat (poultry)	0.01	--	93 / 94	--	2
		0.1	--	94	--	1
		1.0	--	89 / 93	--	2

Reference (analyte)	Matrix	Fortification level [mg/kg]	Recovery rate [%]		cv [%]	n
(thiamethoxam)	milk	0.005	98	71 - 122	12	22
		0.05	91	83 - 96	84- 97	5
		0.1	93	90 - 98	4	7
		0.2	89	80 - 93	6	5
		0.5	88	83 - 91	4	5

Reference (analyte)	Matrix	Fortification level [mg/kg]	Recovery rate [%]		cv [%]	n
(CGA 322704)	milk	0.005	96	72 -113	11	22
		0.05	92	84 - 97	6	5
		0.1	96	90 - 102	5	7
		0.2	92	83 - 95	5	5
		0.5	92	90 - 94	2	5
(thiamethoxam)	kidney (cow)	0.01	102	84 - 113	14	4
		0.1	--	91	--	1
		0.2	--	81	--	1
(CGA 322704)	kidney (cow)	0.01	96	84 - 106	15	4
		0.1	--	88	--	1
		0.2	--	84	--	1
(thiamethoxam)	liver (cow)	0.01	78	73 - 87	11	3
		0.05	--	78	--	1
		0.1	--	87	--	1
		0.5	--	77	--	1
(CGA 322704)	liver (cow)	0.01	80	72 - 94	15	3
		0.05	--	71	--	1
		0.1	--	89	--	1
		0.5	--	80	--	1
(thiamethoxam)	omental fat /	0.01	--	77 / 85	--	1/1

Reference (analyte)	Matrix	Fortification level [mg/kg]	Recovery rate [%]		cv [%]	n
	perinal fat(cow)	0.1	--	88 / --	--	1/0
		0.2	--	-- / 86	--	0/1
(CGA 322704)	omental fat / perinal fat(cow)	0.01	--	84 / 95	--	1/1
		0.1	--	90 / --	--	1/0
		0.2	--	--/ 90	--	0/1
(thiamethoxam)	round muscle	0.01	81	77 - 84	4	3
		0.05	--	96	--	1
		0.1	--	87	--	1
		0.5	--	79	--	1
(CGA 322704)	round muscle	0.01	84	77 - 92	9	3
		0.05	--	95	--	1
		0.1	--	90	--	1
		0.5	--	83	--	1
(thiamethoxam)	tenderloin muscle	0.01	76	69 - 93	16	3
		0.05	--	86	--	1
		0.1	--	82	--	1
		0.2	--	89	--	1
(CGA 322704)	tenderloin muscle	0.01	75	67 - 96	19	3
		0.05	--	86	--	1
		0.1	--	84	--	1
		0.2	--	91	--	1
(thiamethoxam + CGA 322704)	beef liver	0.01	--	100 / 110	--	1/1
		0.1	--	87 / 88	--	1/1
	eggs	0.01	--	90 / 90	--	1/1
		0.1	--	100 / 82	--	1/1
	milk	0.005	--	100 / 100	--	1/1
		0.02	--	100 / 100	--	1/1

Note: at least one blank sample for each matrice and set of fortifications was performed.

Reproducibility of the method has been demonstrated for liver and milk by independent laboratory validation.

Conclusions: LOQ = 0.01 ppm for most matrices except for milk (LOQ = 0.005 ppm). This method allows the determination of thiamethoxam and its major metabolite CGA-322704. Also validation for the analysis of poultry metabolite CGA-265307 are included. Independent laboratory validation include whole milk.

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	June 2005
Materials and methods	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	[redacted]

5.1. Function

Thiamethoxam is an insecticide (PT18).

5.2 Organism(s) to be controlled and products, organisms or objects to be protected

5.2.1. Organism(s) to be controlled

Control of ants, cockroaches and other insects in buildings. Thiamethoxam is formulated as a water dispersible granule (WG) formulation and is applied by hand-held spray equipment.

Control of house flies in animal housings. Thiamethoxam is formulated as a granular bait (GB) ready to use formulation and applied to surfaces as a scatter bait or t boards which are hung inside animal houses. TMX is also formulated as a WG formulation which is mixed with water and painted into surfaces.

5.2.2. Products, objects or organisms to be protected

Frame formulations Optigard LT (WG containing 25% w/w thiamethoxam), Agita 1 GB (containing 1% w/w thiamethoxam) and Agita 10 WG (granules containing 10% w/w thiamethoxam) are used as the typical formulations. However, as seen by the use pattern, various formulations/mixtures will be registered at the Member State level.

5.3. Effects on target organisms, and likely concentration at which the active substance will be used

5.3.1. Effects on target organisms

Activity has been demonstrated against other pests such as ants, cockroaches and house flies.

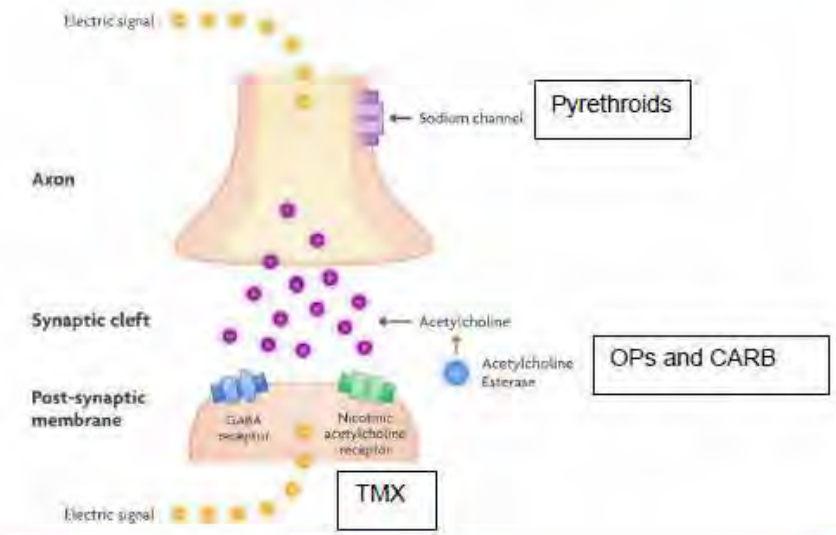
5.4. Mode of action (including time delay)

5.4.1. Mode of action

There is evidence that thiamethoxam interacts with the receptor protein of nicotinic acetyl choline receptors in the nerve cell membrane. TMX has a completely different mode of action to carbamates,

organophosphates, and pyrethroids. The latter bind to the sodium channel in nerves, the first two on the enzyme acetylcholine esterase necessary for the degradation of acetylcholine in the synaptic claft.

Fig. 1: Simple sketch of a nerve synapse



5.4.2. Time delay

Although death can be delayed for up to 24 hours, the intoxicated insect irreversibly stops feeding and is thus comparable to knock-down substances.

5.5. Field of use envisaged

Insecticides, acaricides and products to control other arthropods (PT 18)

5.6. User: industrial, professional, general public (non-professional)

Thiamethoxam containing products are used by professional users

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

5.7.1. Development of resistance

As a general rule the risk of insecticide resistance developing in a given insect pest is related to three factors:

• The lifecycle of the target pest

• The fecundity of the target pest, how many reproductively competent offspring each female can produce

• The degree of exposure to a given class of insecticide

General PPM pests fall into two groups, those with a short lifecycle and many offspring per generation, such as house flies, and those with longer lifecycle and fewer reproductively competent offspring per generation, e.g. ants.

Thiamethoxam is suitable for the control of flies and has a low potential for cross-resistance.

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).

Exposure of multiple generations of insect to insecticides from the same mode of action class will also increase the risk that insecticide susceptibility will fall. Pest species that are exposed to different classes of insecticide, either in temporal rotation or in a spatial mosaic have a reduced risk of losing susceptibility to a given class of insecticides.

As a result of the fast generation time and large number of offspring houseflies can produce, there is a history of insecticide resistance developing. This highlights the importance of having insecticides with different modes of action available for control of houseflies. By following insecticide resistance management (IRM) principles the risk of insecticide resistance development is reduced for all insecticides used. The first steps in an IRM programme are to take all non-insecticide based actions that will reduce the pest pressure, only then should insecticides in a planned rotation or mosaic be employed.

Ants, and occasional invasive pests, e.g. silverfish, woodlice, spiders, etc. are much less likely to develop insecticide resistance due to their longer lifecycle and only occasional exposure to insecticides. In the case of ants the small number of reproductive, as opposed to sterile workers, in a population greatly reduces the risk of insecticide resistance development. German cockroaches lie closer to flies in their risk of insecticide resistance development due to their relatively short lifecycles and fecundity. This is borne out by the incidence of resistance to the older insecticide chemistries. However, reports of resistance to the newer compounds which are often applied in baits are often related to the phenomena of bait aversion, rather than true resistance. That is, the cockroaches avoid exposure to the insecticide in the bait due the detection of a component of the bait matrix, e.g. glucose. A change of bait matrix restores susceptibility. The larger cockroaches, e.g. American or Oriental, with their longer lifecycles and lower fecundity have a much reduced risk of insecticide resistance developing. Again borne out by the limited number of recorded cases. Again, as with houseflies, the key to IRM is to have insecticides with different modes of action available to prevent the pest being exposed to the same mode of action for an extended number of generations.

Section A5.10.1 **Efficacy Data**
Annex Point IIA5.10.1 *insecticide, laboratory study*
TNsG: Pt. I-A5.10.1, Pt. III-Ch. 6

Official use only

41 REFERENCE

1.1	**Reference**	Anonymous (2001): Susceptibility to thiamethoxam in Danish field populations of houseflies *Musca domestica*. Ministry of Food, Agriculture and Fisheries, Denmark, report no. 01-2001, February 2001
1.2	**Data protection**	Yes
1.2.1	Data owner	Novartis Animal Health Inc.
1.2.2	Criteria for data protection	Data submitted on existing a.s. for the purpose of Annex I inclusion.
1.3	**Guideline study**	no international guideline established
1.4	**Deviations**	not applicable

2 METHOD

2.1	**Test Substance (Biocidal Product)**	
2.1.1	Trade name/ proposed trade name	Proposed trade name of the product : thiamethoxam~~Agita~~
2.1.2	Composition of product tested	thiamethoxam, technical material [redacted]
2.1.3	Physical state and nature	solid
2.1.4	Monitoring of active substance concentration	no
2.1.5	Method of analysis	not applicable
2.2	**Reference substance**	dimethoate (organophosphates) batch 20224-00 purity 96-98% azamethiphos (organophosphates) batch 062046/95021 purity 96.5% bioresmethrin (pyrethroid) batch Roussel Uclaf purity 95% methomyl (carbamate) batch 8069-502 purity 98.7%
2.2.1	Method of analysis for reference substance	not relevant
2.3	**Testing procedure**	
2.3.1	Test population / inoculum / test organism	*Musca domestica* standard WHO strain and field populations collected from 20 farms (for more information see Table 5.10_01-1)
2.3.2	Test system	cylindrical paper cage of 500 cm^3 (for details see Table 5.10_01-2)

Section A5.10.1 **Efficacy Data**
Annex Point IIA5.10.1 *insecticide, laboratory study*
TNsG: Pt. I-A5.10.1, Pt. III-Ch. 6

2.3.3	Application of TS	Adult male houseflies were fed 2-3 days granular sugar containing the insecticide at a range of doses (for more details see Table 5.10_01-3). The reference substances dimethoate and bioresmethrin were tested in a contact test (topical application to the dorsal thorax).
2.3.4	Test conditions	25-26°C, 60-65% relative humidity, continuous light
2.3.5	Duration of the test/ Exposure time	72 hours
2.3.6	Trial design	20 to 30 batches of 20 flies were used at 10 to 13 concentrations
2.3.7	Number of replicates performed	not given
2.3.8	Controls	untreated sugar
2.4	**Examination**	
2.4.1	Effect investigated	mortality
2.4.2	Method for recording / scoring of the effect	counting of dead flies at different concentrations to obtain lethal concentrations (LC_{50} and LC_{95} -values) and investigation of the resistance of field strains compared to WHO standard strain A resistance factor (RF) was calculated by dividing the lethal concentration of the field populations by the lethal concentration of the WHO standard strain.
2.4.3	Intervals of examination	24, 48 and 72 hours
2.4.4	Statistics	The observed mortality was corrected by the control mortality according to ABBOTT. Corrected data were then used to calculate the LD_{50} and LD_{95} - respective the LC_{50} and LC_{95} -values by means of probit analysis. Analysis of variance (ANOVA) was done where applicable (homogeneity of data) or GLM F test on unbalanced data sets. Duncan's multiple range test was used to compare treatment means.
2.4.5	Post monitoring of the test organism	not applicable
		3 RESULTS
3.1	**Efficacy**	
3.1.1	Dose/Efficacy curve	Dose/Efficacy curves can be derived from table 3.5
3.1.2	Begin and duration of effects	not specified
3.1.3	Observed effects in the post monitoring phase	not applicable
3.2	**Effects against organisms or objects to be protected**	An LC_{95} was achieved with a concentration of 0.0023% in WHO standard strain of *Musca domestica* and between 0.004% and 0.071% in field populations demonstation that thiamethoxam is highly effective against house flies.
3.3	**Other effects**	none

Section A5.10.1
Annex Point IIA5.10.1
TNsG: Pt. I-A5.10.1, Pt. III-Ch. 6

Efficacy Data
insecticide, laboratory study

3.4 Efficacy of the reference substance

not relevant, since no direct comparison with thiamethoxam

3.5 Tabular and/or graphical presentation of the summarised results

Mortality after 72 hours, concentration given in %
(resistance factors RF based on LC_{50} and LC_{95}-values)

Strain	LC_{50}	LC_{95}	RF50	RF95
WHO	0.0006	0.0023	-	-
303	0.0015	0.011	3	5
357	0.0045	0.071	8	31
381	0.0014	0.012	2	5
662	0.0049	0.054	8	23
767	0.0030	0.020	5	9
791	0.0024	0.0095	4	4
812	0.0035	0.015	6	7
817	0.0017	0.006	3	3
818	0.0018	0.0079	3	3
819	0.0015	0.0048	2	2
820	0.0029	0.012	5	5
821	0.0018	0.012	3	5
822	0.0023	0.012	4	5
823	0.0044	0.044	7	19
824	0.0020	0.019	3	8
825	0.0024	0.012	4	5
826	0.0055	0.013	9	6
827	0.0013	0.0055	2	2
828	0.0052	0.013	9	6
829	0.0011	0.0044	2	2

The level of tolerance varied between the different field strains. Resistance factors of 2 to 9 (based on LC_{50}) and 2 to 31 (based on LC_{95}) were calculated.

3.6 Efficacy limiting factors

3.6.1 Occurrences of resistances

A mortality of 95% was achieved with very low concentrations of thiamethoxam indicating that resistance did not occur (LC_{95} = 0.0023% in WHO standard strain, LC_{95} between 0.004% and 0.071% in field populations). Moreover, there was no indication of cross-resistance between thiamethoxam and any of the other insecticides tested.

3.6.2 Other limiting factors

no indications in the report

Section A5.10.1 **Efficacy Data**
Annex Point IIA5.10.1 *insecticide, laboratory study*
TNsG: Pt. I-A5.10.1, Pt. III-Ch. 6

		4 RELEVANCE OF THE RESULTS COMPARED TO FIELD CONDITIONS
4.1	**Reasons for laboratory testing**	The efficacy can be tested in comparison with a standard strain and under standardised, controlled conditions.
4.2	**Intended actual scale of biocide application**	for the control of flies in animal housing
4.3	**Relevance compared to field conditions**	The susceptibility/ resistance of a WHO standard strain and field populations to thiamethoxam and the investigation of possible cross-resistance to traditional insecticides indicate the efficacy of thiamethoxam. Therefore, this study is relevant to evaluate the performance of products containing thiamethoxam under field conditions.
4.4	**Relevance for read-across**	relevant for read-across
		5 APPLICANT'S SUMMARY AND CONCLUSION
5.1	**Materials and methods**	The efficacy of thiamethoxam technical to WHO standard strain and field populations of *Musca domestica* from 20 farms was investigated. Thiamethoxam was tested in a feeding study and compared to other insecticides (either tested in feeding study or contact test after topical application).
5.2	**Reliability**	~~1~~2
5.3	**Assessment of efficacy, data analysis and interpretation**	Thiamethoxam is highly effective against all strains of flies as indicated by very low concentrations leading to 95% mortality. However, for three field populations higher resistance factors were noticed (19, 23 and 31). There was no indication of cross-resistance between thiamethoxam and any of the other insecticides tested.
5.4	**Conclusion**	Thiamethoxam is suitable for the control of flies and has a low potential for cross-resistance.
5.5	**Proposed efficacy specification**	excellent efficacy

Section A5.10.1 **Efficacy Data**
Annex Point IIA5.10.1 *insecticide, laboratory study*
TNsG: Pt. I-A5.10.1, Pt. III-Ch. 6

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	December 2008
Comments	[redacted]
Summary and conclusion	[redacted]

Table 5.10_01-1: Test organism

Criteria	Details
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

Table 5.10_01-2: Test system

Criteria	Details
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Table 5.10_01-3: Application of test substance

Criteria	Details
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Table 5.10_01-4: Test conditions

Criteria	Details
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Section A 5.10.2 Annex Point IIA V.5.11		Efficacy data Insecticides (in and around buildings)	
		91 REFERENCE	Official use only
1.1	**Reference**	Weeks, S. (2003). Efficacy of residual deposits of thiamethoxam against the pharoah ant. Syngenta Crop Protection report no. 1P/01/014, 27 February, 2003 (unpublished).	
1.2	**Data protection**	Yes.	
1.2.1	Data owner	Syngenta Crop Protection.	
1.2.2	Companies with letter of access	[redacted].	
1.2.3	Criteria for data protection	[redacted]	
1.3	**Guideline study**	No.	
1.4	**Deviations**	Not applicable.	
		2 METHOD	
2.1	**Test Substance (Biocidal Product)**	As given in Section B 2.	
2.1.1	Trade name/ proposed trade name	Thiamethoxam	
2.1.2	Composition of Product tested	Technical material.	
2.1.3	Physical state and nature	Off-white powder (as given in Section A 2).	
2.1.4	Monitoring of active substance concentration	No.	
2.1.5	Method of analysis	Not applicable.	
2.2	**Reference substance**	Lambda-cyhalothrin, beta-cyfluthrin, fipronil and imidacloprid.	
2.2.1	Method of analysis for reference substance	No.	
2.3	**Testing procedure**		
2.3.1	Test population / inoculum / test organism	See Table B 5.10.2-11 and B 5.10.2-12 below.	
2.3.2	Test system	See Table B 5.10.2-13 below.	
2.3.3	Application of TS	See Table B 5.10.2-14 below.	
2.3.4	Test conditions	See Table B 5.10.2-15 below.	

Section A 5.10.2 Annex Point IIA V.5.11		Efficacy data Insecticides (in and around buildings)	
2.3.5	Duration of the test / Exposure time	Until complete insect knockdown was seen or for 60 minutes.	
2.3.6	Number of replicates performed	Three.	
2.3.7	Controls	None.	
2.4	**Examination**		
2.4.1	Effect investigated	Speed of mortality.	
2.4.2	Method for recording / scoring of the effect	Observation of mortality.	
2.4.3	Intervals of examination	Continuous for 60 minutes.	
2.4.4	Statistics	None.	
2.4.5	Post monitoring of the test organism	No.	
		3 RESULTS	
3.1	**Efficacy**	Residual deposits of thiamethoxam were effective in controlling workers of the Pharaoh ant, *Monomorium pharaonis*. Estimated knock down times were slower for thiamethoxam than those for lambda-cyhalothrin and beta-cyfluthrin but faster than both imidacloprid and fipronil.	
3.1.1	Dose/Efficacy curve	There was a trend to faster knock down at higher concentrations of thiamethoxam, but the effect was not always consistent.	
3.1.2	Begin and duration of effects	Estimated knock down times (KD90 values) of worker ants were 17 and 18 minutes following exposure to 10 or 100 ppm thiamethoxam, respectively, applied to glass vials.	
3.1.3	Observed effects in the post monitoring phase	Not recorded.	
3.2	**Effects against organisms or objects to be protected**	Not recorded.	
3.3	**Other effects**	Not applicable.	
3.4	**Efficacy of the reference substance**	Lambda-cyhalothrin, beta-cyfluthrin, imidacloprid and fipronil also controlled *Monomorium pharaonis* (as assessed by knock down).	
3.5	**Tabular and/or graphical**	A summary of the speed of kill of *Monomorium pharaonis* is presented below.	

Section A 5.10.2 Annex Point IIA V.5.11	**Efficacy data** Insecticides (in and around buildings)	
	***Monomorium pharaonis* speed of kill**	

Rate (ppm)	KD 90 (minutes)				
	Thia-methoxam	Beta-cyfluthrin	Lambda-cyhalothrin	Imidacloprid	Fipronil
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]					

3.6	**Efficacy limiting factors**		
3.6.1	Occurrences of resistances	None stated.	
3.6.2	Other limiting factors	None.	

Section A 5.10.2 **Annex Point IIA V.5.11**		**Efficacy data** Insecticides (in and around buildings)	
		4 RELEVANCE OF THE RESULTS COMPARED TO FIELD CONDITIONS	
4.1	**Reasons for laboratory testing**	Not applicable.	
4.2	**Intended actual scale of biocide application**	The concentrations applied were lower than the intended use rate concentration (2 g a.s./L).	
4.3	**Relevance compared to field conditions**		
4.3.1	Application method	1 mL of thiamethoxam was applied in acetone to a glass vial. The glass vial was rolled until the acetone evaporated.	
4.3.2	Test organism	Pharoah ant *Monomorium Pharaonis* is representative of the target organism of intended use (ant).	
4.3.3	Observed effect	Observed effect was indicative of the desired effect in field applications.	
4.4	**Relevance for read-across**	Yes.	
		5 APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	1 mL of thiamethoxam was applied in acetone to a glass vial. The glass vial was rolled until the acetone evaporated. Concentrations tested of thiamethoxam and the other test substances ranged from 0.001 to 1000 ppm. Insects were exposed to treated glass vials until complete knockdown was seen or for 60 minutes.	
5.2	**Reliability**	The methods used and the test results are reliable and relevant for efficacy assessment. Reliability indicator 2.	
5.3	**Assessment of efficacy, data analysis and interpretation**	Estimated knock down times (KD90) of worker ants were 17 and 18 minutes following exposure to 10 or 100 ppm thiamethoxam applied to glass vials. There was a trend to faster knock down at higher concentrations of thiamethoxam, but the effect was not always consistent.	
5.4	**Conclusion**	Estimated knock down times were slower for thiamethoxam than those for lambda-cyhalothrin and beta-cyfluthrin but faster than both imidacloprid and fipronil.	
5.5	**Proposed efficacy specification**	The efficacy of the product was acceptable in the test.	
		Evaluation by Competent Authorities	
		EVALUATION BY RAPPORTEUR MEMBER STATE	
Date		December 2008	

Section A 5.10.2 Annex Point IIA V.5.11	Efficacy data Insecticides (in and around buildings)	
Comments	[redacted]	
Summary and conclusion	[redacted]	

Tables for Method

Table B 5.10.2-11: (mixed) Population / Inoculum

Criteria	Details
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Table B 5.10.2-12: Test organism

Criteria	Details
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Table B 5.10.2-13: Test system

Criteria	Details
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Table B 5.10.2-14: Application of test substance

Criteria	Details
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Table B 5.10.2-15: Test conditions

Criteria	Details
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Section A 5.10.3 **Annex Point IIB V.5.11**		**Efficacy data** Insecticides (in and around buildings)	
		1 REFERENCE	**Official use only**
1.1	**Reference**	Weeks, S., Cross, N (2002). Thiamethoxam: Intrinsic activity against German and American cockroaches. Syngenta Crop Protection report no. 1P/01/012, 22 October, 2002 (unpublished).	
1.2	**Data protection**	Yes.	
1.2.1	Data owner	Syngenta Crop Protection.	
1.2.2	Companies with letter of access	[redacted]	
1.2.3	Criteria for data protection	[redacted]	
1.3	**Guideline study**	No.	
1.4	**Deviations**	Not applicable.	
		2 METHOD	
2.1	**Test Substance (Biocidal Product)**	As given in Section B 2.	
2.1.1	Trade name/ proposed trade name	Thiamethoxam	
2.1.2	Composition of Product tested	Technical material.	
2.1.3	Physical state and nature	Off-white powder (as given in Section A 2).	
2.1.4	Monitoring of active substance concentration	No.	
2.1.5	Method of analysis	Not applicable.	
2.2	**Reference substance**	Lambda-cyhalothrin, beta-cyfluthrin, imidacloprid and fipronil.	
2.2.1	Method of analysis for reference substance	No.	
2.3	**Testing procedure**		
2.3.1	Test population / inoculum / test organism	See Table B 5.10.2-16 and B 5.10.2-17 below.	
2.3.2	Test system	See Table B 5.10.2-18 below.	
2.3.3	Application of TS	See Table B 5.10.2-19 below.	
2.3.4	Test conditions	See Table B 5.10.2-20 below.	
2.3.5	Duration of the test / Exposure time	2 days.	
2.3.6	Number of replicates	Not stated.	

Section A 5.10.3 Annex Point IIB V.5.11		Efficacy data Insecticides (in and around buildings)	
	performed		
2.3.7	Controls	None.	
2.4	**Examination**		
2.4.1	Effect investigated	Mortality.	
2.4.2	Method for recording / scoring of the effect	Observation of mortality.	
2.4.3	Intervals of examination	One and two days after application.	
2.4.4	Statistics	Logit analysis & logarithmic calculations.	
2.4.5	Post monitoring of the test organism	No.	
		3 RESULTS	
3.1	**Efficacy**	Thiamethoxam demonstrated significant biological activity against the German cockroach, *B. germanica,* and moderate activity against the American cockroach, *P.americana.* Thiamethoxam was intrinsically less active than beta-cyfluthrin, lambda-cyhalothrin and fipronil against both cockroach pest species, but caused greater mortality than imidacloprid against both *species.*	
3.1.1	Dose/Efficacy curve	Not applicable.	
3.1.2	Begin and duration of effects	Thiamethoxam applied directly to adult males demonstrated significant biological activity against the German cockroach, *B. germanica* and moderate activity against the American cockroach, *P.americana.* Mortality assessments were carried out at 1 and 2 days after treatment.	
3.1.3	Observed effects in the post monitoring phase	Not recorded.	
3.2	**Effects against organisms or objects to be protected**	Not recorded.	
3.3	**Other effects**	Not applicable.	
3.4	**Efficacy of the reference substance**	Beta-cyfluthrin, lambda-cyhalothrin, imidacloprid and fipronil were also active against both cockroach species.	
3.5	**Tabular and/or**	A summary of the results is presented below.	

Section A 5.10.3 **Annex Point IIB V.5.11**	**Efficacy data** Insecticides (in and around buildings)		

Efficacy against adult male *Blattella germanica*

Test material	2 days after treatment	
	LC_{50} (ppm)	**LC_{90} (ppm)**
Thiamethoxam	13.95	68.69
Lambda-cyhalothrin	6.24	14.89
Fipronil	0.83	2.93
Beta-cyfluthrin	3.12	5.79
Imidacloprid	58% @ 1,000 ppm	

Efficacy against adult male *Periplaneta americana*

Test material	2 days after treatment	
	LC_{50} (ppm)	**LC_{90} (ppm)**
Thiamethoxam	70% @ 1,000 mg/kg	
Lambda-cyhalothrin	20 - 30	30 – 40
Fipronil	450	1,000
Beta-cyfluthrin	30 - 40	40 – 50
Imidacloprid	25% @ 1,000 ppm	

3.6	**Efficacy limiting factors**	
3.6.1	Occurrences of resistances	None stated.
3.6.2	Other limiting factors	None.

Section A 5.10.3 **Annex Point IIB V.5.11**		**Efficacy data** Insecticides (in and around buildings)	
		4 RELEVANCE OF THE RESULTS COMPARED TO FIELD CONDITIONS	
4.1	**Reasons for laboratory testing**	Not applicable.	
4.2	**Intended actual scale of biocide application**	The intended use rate concentration is 2 g a.s./L.	
4.3	**Relevance compared to field conditions**		
4.3.1	Application method	1 mL of each chemical was applied directly to each insect.	X1
4.3.2	Test organism	German cockroach, *B. germanica* and American cockroach, *P.americana* are representative of the target organism of intended use (cockroach).	
4.3.3	Observed effect	Observed effect was comparable to desired effect in field applications.	
4.4	**Relevance for read-across**	Yes.	
		5 APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	Thiamethoxam was applied directly to each insect.	
5.2	**Reliability**	The methods used and the test results are reliable and relevant for efficacy assessment. Reliability indicator 2.	
5.3	**Assessment of efficacy, data analysis and interpretation**	Thiamethoxam demonstrated significant biological activity against the German cockroach, *B. germanica* and moderate activity against the American cockroach, *P.americana*. Thiamethoxam was intrinsically less active than beta-cyfluthrin, lambda-cyhalothrin, and fipronil against both cockroach pest species, but caused greater mortality than imidacloprid against both species.	
5.4	**Conclusion**	Thiamethoxam demonstrated significant biological activity against the German cockroach, *B. germanica* and moderate activity against the American cockroach, *P.americana*.	
5.5	**Proposed efficacy specification**	The efficacy of the product was acceptable in the test.	
		Evaluation by Competent Authorities	
		EVALUATION BY RAPPORTEUR MEMBER STATE	
Date		December 2008	
Comments		[redacted]	

Section A 5.10.3 Annex Point IIB V.5.11	Efficacy data Insecticides (in and around buildings)	
Summary and conclusion	[redacted]	

Tables for Method

Table B 5.10.2-16: (mixed) Population / Inoculum

Criteria	Details
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Table B 5.10.2-17: Test organism

Criteria	Details
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Table B 5.10.2-18: Test system

Criteria	Details
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Table B 5.10.2-19: Application of test substance

Criteria	Details
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Table B 5.10.2-20: Test conditions

Criteria	Details
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Section A5.10.4
Annex Point IIA5.10.1
TNsG: Pt. I-A5.10.1, Pt. III-Ch. 6

Efficacy Data
insecticide, laboratory study

			Official use only
		1 REFERENCE	
1.1	**Reference**	*Musca domestica:* laboratory bioassay methodology for neonicotinoids (1998)	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Novartis Animal Health Inc.	
1.2.2	Criteria for data protection	[redacted]	
1.3	**Guideline study**	no international guideline established	
1.4	**Deviations**	not applicable	
		2 METHOD	
2.1	**Test Substance (Biocidal Product)**	Thiamethoxam (CGA 29343): 100% Imidacloprid (CGA 256084): 100% Nitenpyram (CGA 246913): 99.9% CGA 293343 10WG (thiamethoxam 10%): was used in the residual test	
2.1.1	Trade name/ proposed trade name	See 2.1	
2.1.2	Composition of product tested	See 2.1	
2.1.3	Physical state and nature		
2.1.4	Monitoring of active substance concentration		
2.1.5	Method of analysis		
2.2	**Reference substance**	azamethiphos	
2.2.1	Method of analysis for reference substance		
2.3	**Testing procedure**		
2.3.1	Test population / inoculum / test organism	The standard susceptible WHO/1 strain of *Musca domestica*	
2.3.2	Test system		
2.3.3	Application of TS	Topical, feeding, residual deposit	
2.3.4	Test conditions	**Topical bioassay** 3 to 6 day old flies are removed from the cages with test tubes. These are cooled for about 1 hour in ice to immobilise the insects for handling. The insects are then sexed on a cooling table, females are returned to the ice and males used for the feeding test or discarded. On another cooling table, using a Hamilton micro dispenser, 1µl acetone solution was	

Section A5.10.4 Annex Point IIA5.10.1 TNsG: Pt. I-A5.10.1, Pt. III-Ch. 6	Efficacy Data *insecticide, laboratory study*	
		applied onto the dorsal thorax of each female fly. For each concentration 2 tests of 10 flies are treated. The insects are then placed in a plastic yoghurt beaker with a gauze lid. A dental plug soaked in 2% sugar solution is placed on top of the gauze as water source. Bioassay conditions are 22ºC and 55% RH with a light intensity of about 500-600 lux during the day. Flies are counted as dead if they are unable to stand on 3 feet. **Feeding bioassays** 3 to 6 day old flies are collected from the rearing cages with test in test-tubes which are then placed in crushed ice. The immobilised insects are sexed, counted into sets of 25 males and transferred to the test units. These units of 1700ml cylindrical Plexiglas cages with paper walls and net lids. Approximately 0.5g impregnated sugar is presented in small petri dishes as the only food. Water is supplied in cotton-plugged vials. The bioassays are carried out at 22ºC and 55%RH. Each concentration was tested with 2 sets of 25 flies. Departures from this standards method are noted in the results section. **Residual deposit bioassay** Unsexed flies are exposed to the deposits on hardboard panels in cylinders as in the feeding method. Conditions are made in the same way. The CGA 293343 10WG formulation was mixed 1:1, 1:9 and 0.1:9.9 with water to give 5%, 1% and 0.1% active ingredient at application. Spots of 10 cm diameter were painted to "run off" onto the smooth side of 11cm x 11 cm hardboard panels. Spots on control panels were painted with sugar solutions.
2.3.5	Duration of the test/ Exposure time	
2.3.6	Trial design	
2.3.7	Number of replicates performed	
2.3.8	Controls	no
2.4	**Examination**	
2.4.1	Effect investigated	evaluate an appropriate bioassay methodology for the neonicotinoids
2.4.2	Method for recording / scoring of the effect	
2.4.3	Intervals of examination	**Topical bioassay** Mortality counts are made 24 and 48 hours **Feeding bioassays and Residual deposit bioassay** Mortality counts are made 24 and 48 and in some case also 72 hours
2.4.4	Statistics	Test concentrations were used which would enable a log.dose/probit-response regression line and lethal dose or concentration levels to be calculated. The SAS analyses gives: 1) slope ± SE (standard error) and 2) $LD(LC)_{50/95}$ values with CI (confidence intervals)
2.4.5	Post monitoring of	

Section A5.10.4 Annex Point IIA5.10.1 TNsG: Pt. I-A5.10.1, Pt. III-Ch. 6	Efficacy Data *insecticide, laboratory study*

the test organism

3 RESULTS

3.1 Efficacy

Experiments were initiated to evaluate an appropriate bioassay methodology for the neonicotinoids; CGA 29343, imidacloprid and nitenpyram, against *Musca domestica*. Topical application was given preference although earlier results were weak. Supplementary feeding experiments and residual deposit tests were made with CGA 29343.

3.1.1 Dose/Efficacy curve

Topical bioassays

CGA 293343, imidacloprid and nitenpyram showed little activity (LD_{50} values >1000ng/insect) if applied topically in acetone to individual flies of susceptible WHO/1 strain. Efficacy could be significantly improved by the use of 20% olive oil in the acetone. Baselines could then be established for 3 chemicals. CGA 293343 was clearly the most effective compound followed by imidacloprid. Nitenpyram was less effective and the regression line was unclear. The summarised results are presented in table 1 and figure 1 (see point 3.5). CGA 293343 dissolved in acetone/olive oil was applied at the expected LD90 of 200ng. Either the: 1) thorax, 2) head, 3) proboscis or 4) tarsi (one-sixth of the dose on each) were treated. None of the positions resulted in 100% mortality suggesting no real improvement in effect (see table 2).

Feeding bioassay with CGA 293343

Sugar baits were prepared from the acetonic solutions of CGA 293343. The baseline was established for the susceptible WHO/1 strain. Three independent experiments were run for 72 h. Mortality counts were made each day. Probit analyses for pooled data are summarised in table 3.

Residual deposit bioassay

A preliminary test was made to see if the artificial bioassays above convert into real control with practical formulation. The flies were exposed to the deposits of CGA 293343 10WG. The normal deposits showed full activity. Further lower concentrations of the formulation were less active. The results are summarised in table 4.

3.1.2 Begin and duration of effects

3.1.3 Observed effects in the post monitoring phase

3.2 Effects against organisms or objects to be protected

3.3 Other effects

The standard topical application method, with the addition of 20% olive oil to the acetone should therefore be used to compare strains.

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Annex Point IIA5.10.1
TNsG: Pt. I-A5.10.1, Pt. III-Ch. 6

Efficacy Data

insecticide, laboratory study

3.4 Efficacy of the reference substance

The published LD_{50} for the standard, azamethiphos, 40ng using acetone alone. The standard topical application is made onto dorsal thorax of flies. Another position might be better for neonicotinoids. Treatment between the legs was earlier reported as not improving effectiveness of CGA 293343. An attempt was therefore made to locate other points on the fly which would give higher activity.

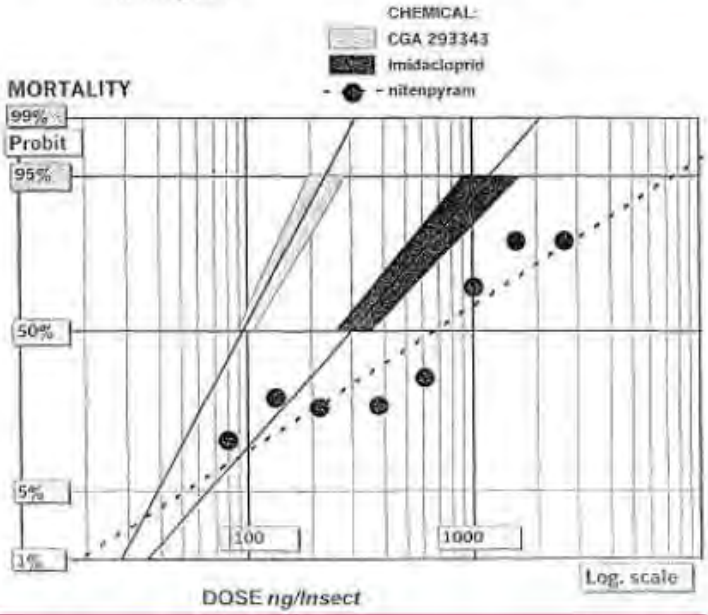
3.5 Tabular and/or graphical presentation of the summarised results

Table 1: Probit analysis of 24h mortalities, Lethal Dose in ng active ingredient per insect

ADDITIVE	n	SLOPE (± SE)	LD_{50} (95% CI)	LD_{95} (95% CI)
CGA 293343				
None*	90	1.4 ±0.29	1900 (800-290??)	>3200
Olive oil	420	4.5 ±0.48	98 (91-110)	230 (200-280)
imidacloprid				
None	120		>>1000	>>1000
Olive oil	420	2.8 ± 0.38	300 (250-350)	1200 (920-1,700)
nitenpyram **				
None	80		>>1000	>>1000
Olive oil	460	1.6 ± 0.34	680	7300

*Reported earlier ** Not a line see figure 1

Figure 1: Regression lines for CGA 293343, imidacloprid and nitenpyram



Section A5.10.4
Annex Point IIA5.10.1
TNsG: Pt. I-A5.10.1, Pt. III-Ch. 6

Efficacy Data
insecticide, laboratory study

Table 2: Percentage mortality (ABBOTT corrected) 24h after application of 200ng CGA 293343 onto WHO flies.

APPLICATION POINT	µl SOLUTION APPLIED	PERCENTAGE MORTALITY
Thorax	1	89
Head	0.1	85
Proboscis	0.1	70
Leg	5 x 0.1	90

Table 3: Probit analysis of 24h mortalities, lethal concentration (LC) in ppm on sugar.

STRAIN	n°	COUNTS HOURS	SLOPE (±SE)	LC_{50} (95% CI)	LC_{90} (95% CI)
WHO/1	280	24	2.7 ± 0.21	50 (54-68)	250 (200-340)
		48	2.8 ± 0.22	40 (36-44)	160 (130-200)
		72	2.9 ± 0.23	31 (28-35)	120 (98-150)

Table 4: Percentage mortality (ABBOTT corrected) 24h and 48h after start of facultative exposure to CGA 293343 treated boards.

A.I. CONCENTRATION IN PAINT	MORTALITY (%) AFTER HOURS 24	48
5%	92	100
1%	56	68
0.1%	6	26

3.6 Efficacy limiting factors

3.6.1 Occurrences of resistances

3.6.2 Other limiting factors

4 RELEVANCE OF THE RESULTS COMPARED TO FIELD CONDITIONS

4.1 Reasons for laboratory testing

Experiments were initiated to evaluate an appropriate bioassay methodology for the neonicotinoids: CGA 293343, imidacloprid and nitenpyram, against *Musca domestica*.

4.2 Intended actual scale of biocide application

4.3 Relevance compared to field conditions

Section A5.10.4 Annex Point IIA5.10.1 TNsG: Pt. I-A5.10.1, Pt. III-Ch. 6	Efficacy Data *insecticide, laboratory study*
4.4 Relevance for read-across	
	5 APPLICANT'S SUMMARY AND CONCLUSION
5.1 Materials and methods	
5.2 Reliability	2
5.3 Assessment of efficacy, data analysis and interpretation	Appropriate laboratory methodology is needed for bioassays of neonicotinoids against *Musca domestica*. Topical application onto individual insects was given priority. Feeding and residual deposit experiments were also tried out. The poor activity of CGA 293343, imidacloprid and nitenpyram in standard topical test could be improved by adding olive oil to the acetone solvent. Activity was not further improved by altering the application point on the insect. CGA 293343 was, as expected, better than imidacloprid and nitenpyram. Nitenpyram did not give a clear dose/mortality regression line. In the standard feeding experiment, using treated sugar as bait, CGA 293343 gave a clear concentration/mortality regression line. This had, however, a significantly flatter slope than that obtained in the topical test. Residual deposits of formulated (10WG) were active on hardboard. As topical application is now possible, this dose test should be used for comparisons of compounds and fly strains. Higher variance was found, and is to be expected, in concentration tests involving active pick up of the compounds by the insects. Complementary feeding tests will, nevertheless, be needed to address oral-uptake parameters.
5.4 Conclusion	Topical application gives a clear dose/mortality correlation if some oil is added to the acetone. This seems to be the optimal bioassay system. CGA 293343 is the most effective of three neonicotinoids. The regression line for CGA 293343 is significantly steeper than in the feeding test. The few results in the deposit test indicate an even flatter regression line. Higher variance is to be expected in these test systems. This is because activity of the insects themselves determines the rate of pick-up of the toxicant. Feeding tests will nevertheless be needed in some cases to assess the potential of the compounds.
5.5 Proposed efficacy specification	

Section A5.10.4 Annex Point IIA5.10.1 TNsG: Pt. I-A5.10.1, Pt. III-Ch. 6	Efficacy Data *insecticide, laboratory study*
	Evaluation by Competent Authorities
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	February 2011
Comments	
Summary and conclusion	[redacted]

Section A5.10.5
Annex Point IIA5.10.1
TNsG: Pt. I-A5.10.1, Pt. III-Ch. 6

Efficacy Data
insecticide, laboratory study

Official use only

	1 REFERENCE	
1.1	**Reference**	Preliminary bioassays for insecticide resistance in a *Musca domestica* field strain French (2002)
1.2	**Data protection**	Yes
1.2.1	Data owner	Novartis Animal Health Inc.
1.2.2	Criteria for data protection	[redacted]
1.3	**Guideline study**	no international guideline established
1.4	**Deviations**	not applicable
	2 METHOD	
2.1	**Test Substance (Biocidal Product)**	The following chemicals were included in the study: Azamethiphos Diazinon Permethrin Thiamethoxam
2.1.1	Trade name/ proposed trade name	
2.1.2	Composition of product tested	Azamethiphos: 98.2% Diazinon: 91.4% Permethrin: 97% Thiamethoxam: 100%
2.1.3	Physical state and nature	
2.1.4	Monitoring of active substance concentration	
2.1.5	Method of analysis	
2.2	**Reference substance**	
2.2.1	Method of analysis for reference substance	
2.3	**Testing procedure**	
2.3.1	Test population / inoculum / test organism	Pupae of a French *Musca domestica* strain
2.3.2	Test system	
2.3.3	Application of TS	Topical application
2.3.4	Test conditions	Three to six-day-old flies were removed from the rearing cages with test-tubes. These were cooled for about one hour in ice to immobilize

Section A5.10.5 Annex Point IIA5.10.1 TNsG: Pt. I-A5.10.1, Pt. III-Ch. 6	Efficacy Data *insecticide, laboratory study*	
	the insects for handling. The insects were then sexed on a cooling table, females were returned to the ice and males discarded. Applications were also made on the cooling table. Using a Hamilton dispenser, 1µl acetone-chemical solutions were applied onto the dorsal thorax of each female fly. The novel chemical thiamethoxam was diluted in 4 parts acetone and 1part olive oil. For each dose two sets of 10 flies were treated. The insects were then placed in a plastic yogurt beaker with a gauze lid. A dental plug soaked in 2% sugar solution was placed on top of the gauze as water source. Bioassays were kept in incubators with a 12h day-night cycle at 22°C and 55% RH. Flies were counted as "dead" if they were unable to stand on their feet.	
2.3.5 Duration of the test/ Exposure time		
2.3.6 Trial design		
2.3.7 Number of replicates performed		
2.3.8 Controls	no	
2.4 Examination		
2.4.1 Effect investigated	Resistance level	
2.4.2 Method for recording / scoring of the effect		
2.4.3 Intervals of examination	Mortality assessments were made 24 and 48 after application.	
2.4.4 Statistics		
2.4.5 Post monitoring of the test organism		
	3 RESULTS	
3.1 Efficacy	The objective of the study was to determine the resistance level to key chemicals of a French *Musca domestica* field strain	
3.1.1 Dose/Efficacy curve		
3.1.2 Begin and duration of effects	Resistance was seen to the classical standards azamethiphos, diazinon and permethrin. Thiamethoxam (CGA 293343) was active indicating no resistance to novel chemistry. The previously established LD99s of the standard WHO/1 strain were used to set DDs (**D**iscriminating **D**oses). The strain was tested at the DD and multiples of it (4, 16, 64DD). The summary in table 1 shows the DD value for the WHO/1 strain and the obtained percentage mortality values for the FRA flies.	
3.1.3 Observed effects in the post monitoring phase		

Section A5.10.5
Annex Point IIA5.10.1
TNsG: Pt. I-A5.10.1, Pt. III-Ch. 6

Efficacy Data
insecticide, laboratory study

3.2 Effects against organisms or objects to be protected

3.3 Other effects

-

3.4 Efficacy of the reference substance

3.5 Tabular and/or graphical presentation of the summarised results

Table 1: LD_{99} in ng active ingredient per insect of the standard baseline strain and percentage mortality in the FRA strain 24h after application at 1, 4, and when available 16 and 64DD.

CHEMICAL	BASELINE ESTABLISHED	BASELINE LD_{99}	MORTALITY (%) AT LEVEL: DD	4DD	16DD	64DD
Azamethiphos	2001	210	5	0	5	
Diazinon	1990	110	0	0	16	100
Permethrin	1990	100	0	30	60	95
Thiamethoxam*	1998	320	53	95		

* Chemical tested in acetone:olive oil (4:1) instead of acetone alone.

3.6 Efficacy limiting factors

3.6.1 Occurrences of resistances

3.6.2 Other limiting factors

4 RELEVANCE OF THE RESULTS COMPARED TO FIELD CONDITIONS

4.1 Reasons for laboratory testing

A key set of chemical was used in preliminary topical application tests to define insecticide resistance in a french field strain of *Musca domestica*

4.2 Intended actual scale of biocide application

4.3 Relevance compared to field conditions

4.4 Relevance for read-across

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

5.2 Reliability

2

Section A5.10.5 Annex Point IIA5.10.1 TNsG: Pt. I-A5.10.1, Pt. III-Ch. 6	Efficacy Data *insecticide, laboratory study*
5.3 Assessment of efficacy, data analysis and interpretation	
5.4 Conclusion	The results indicate the presence of resistance to the classical adulticides: azamethiphos, diazinon and permethrin: but not to thiamethoxam
5.5 Proposed efficacy specification	

Section A5.10.5 Annex Point IIA5.10.1 TNsG: Pt. I-A5.10.1, Pt. III-Ch. 6	Efficacy Data *insecticide, laboratory study*
	Evaluation by Competent Authorities
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	February 2011
Comments	
Summary and conclusion	[redacted]

Section A 5.10.6	Efficacy data Insecticides (in and around buildings)	
	1 REFERENCE	Official use only
1.1 Reference	Anon. (2003). Control of Argentine ants with Actar 25 WG. La Cruz Test Center of Entomology, Chile June, 2003 (unpublished).	
1.2 Data protection	Yes.	
1.2.1 Data owner	Syngenta Crop Protection.	
1.2.2 Companies with letter of access	None.	
1.2.3 Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of entry into Annex I.	
1.3 Guideline study	No.	
1.4 Deviations	Not applicable.	
	2 METHOD	
2.1 Test Substance (Biocidal Product)	As given in Section B 2.	
2.1.1 Trade name/ proposed trade name	'Optigard LT' (named 'Actara 25 WG' in report).	
2.1.2 Composition of Product tested	250 g a.s./kg WG (as given in Section B 2).	
2.1.3 Physical state and nature	Water dispersible granule formulation (as given in Section B 2).	
2.1.4 Monitoring of active substance concentration	No.	
2.1.5 Method of analysis	Not applicable.	
2.2 Reference substance	Fipronil (Regent 800 WG)	
2.2.1 Method of analysis for reference substance	No.	
2.3 Testing procedure		
2.3.1 Test population / inoculum /	See Tables A5.10.2-01 and A5.10.2-02 below.	

Section A 5.10.6	**Efficacy data** Insecticides (in and around buildings)	
test organism		
2.3.2 Test system	See Table A5.10.2-03 below.	
2.3.3 Application of TS	See Table A5.10.2-04 below.	
2.3.4 Test conditions	See Table A5.10.2-05 below.	
2.3.5 Duration of the test / Exposure time	40 days.	
2.3.6 Number of replicates performed	One.	
2.3.7 Controls	Untreated control (sugared water only).	
2.4 Examination		
2.4.1 Effect investigated	Ant traffic on trees.	
2.4.2 Method for recording / scoring of the effect	Ant traffic was measured by the number of ants climbing tree trunks per unit time. Consumption of bait was also measured.	
2.4.3 Intervals of examination	0 (before application) and 2, 5, 7, 12, 16, 20, 27 and 40 days after application. (One minute observation period.)	
2.4.4 Statistics	None.	
2.4.5 Post monitoring of the test organism	No.	
	3 RESULTS	
3.1 Efficacy	A single application of 'Optigard LT WG' at 0.001 g thiamethoxam/L and 0.1 g thiamethoxam/L to the base of trees resulted in 53-82% and 92-100% control of Argentine ants, respectively, at all assessment dates. The efficacy of the reference substance was 52-96%. The weight of bait in the flasks decreased during the course of the study for all treatments. After 12 days there was no bait remaiing in the untreated flask. After 40 days there was no bait remaining in the treated flasks. The rate of decline of bait was similar for the three treatments.	
3.1.1 Dose/Efficacy curve	Not applicable.	
3.1.2 Begin and duration of effects	'Optigard LT WG' applied at 0.001 g thiamethoxam/L and 0.1 g thiamethoxam/L controlled populations of Argentine ants.	
3.1.3 Observed effects in the post monitoring phase	Not recorded.	

Section A 5.10.6	**Efficacy data** Insecticides (in and around buildings)	
3.2 Effects against organisms or objects to be protected	Not recorded.	
3.3 Other effects	Not applicable.	
3.4 Efficacy of the reference substance	Not applicable.	
3.5 Tabular and/or graphical presentation of the summarised results	A summary of the key results of the study is presented below.	

Time (days)	Mean no. ants/min (% control)				Mean bait consumption (g)			
	Un-treated	Optigard LT 0.001 g/L	Optigard LT 0.1 g/L	Fipronil 0.1g/L	Control	Optigard LT 0.001 g/L	Optigard LT 0.1 g/L	Fipronil 0.1g/L
0 (pre-treat-ment)	[redacted]							
2								
5								
7								
12								
16								
20								
27								
40								

All results are mean of 10 trees per treatment except for results marked with * (9 trees) or ** (8 trees)..

The percentage control is calculated for treatments compared to untreated populations at each assessment date.

3.6 Efficacy limiting factors		
3.6.1 Occurrences of resistances	None stated.	
3.6.2 Other limiting factors	None.	

Section A 5.10.6	**Efficacy data** Insecticides (in and around buildings)	
	4 RELEVANCE OF THE RESULTS COMPARED TO FIELD CONDITIONS	
4.1 Reasons for laboratory testing	Not applicable.	
4.2 Intended actual scale of biocide application	The concentration applied was lower than the intended use rate concentration.	
4.3 Relevance compared to field conditions		
4.3.1 Application method	Application method is comparable to intended use. 'Optigard LT WG'is applied to the site of existing ant infestations.	
4.3.2 Test organism	Test organism (Argentine ant) is representative of the target organism of intended use (ant).	
4.3.3 Observed effect	Observed effect was comparable to desired effect in field applications.	
4.4 Relevance for read-across	Yes.	
	5 APPLICANT'S SUMMARY AND CONCLUSION	
5.1 Materials and methods	A single application of 'Optigard LT WG' applied at 0.001 g thiamethoxam/L or 0.1 g thiamethoxam/L was applied as a sugared bait to the base of 200 orange trees. Ant traffic on the trunks of ten trees was observed over 40 days after application. The weight of bait remaining was measured at each assessment date.	
5.2 Reliability	2	
5.3 Assessment of efficacy, data analysis and interpretation	A single application of 'Optigard LT WG' at 0.001 g thiamethoxam/L or 0.1 g thiamethoxam/L in sugared water applied to the base of orange trees controlled Argentine ants. At 0.001 g thiamethoxam/L, ant numbers were reduced by 53 to 82% in comparison with untreated populations. At 0.1 g thiamethoxam/L, ant numbers were reduced by 92 to 100% in comparison with untreated populations.	
5.4 Conclusion	The study was conducted under commercial conditions and it is concluded that the efficacy of the product (effectiveness) was acceptable.	
5.5 Proposed efficacy specification	The efficacy of the product was acceptable in the test.	
	Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE	

Section A 5.10.6	Efficacy data Insecticides (in and around buildings)	
Date	February 2011	
Comments	[redacted]	
Summary and conclusion	[redacted]	

Tables for Method

Table A5.10.2-01: (mixed) Population / Inoculum

Criteria	Details
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Table A5.10.2-02: Test organism

Criteria	Details
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Table A5.10.2-03: Test system

Criteria	Details
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Table A5.10.2-04: Application of test substance

Criteria	Details
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Table A5.10.2-05: Test conditions

Criteria	Details
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

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

1. Annex point(s)	**IIA, 5.2.1 Acute toxicity - oral**
2. Reference point (location) in dossier	Volume 7, Section 3, Annex IIA, point 5.2.1 / 01
3. Authors (year) **Title** **Owner, Date**	[redacted] An acute oral toxicity study of CGA 293'343 tech. in rats. Syngenta Crop Protection AG, unpublished report No. B-3120, CG 942111, May 23, 1996
4. Testing facility	[redacted]
5. Dates of work	October 17, 1995 - October 31, 1995
6. Test substance	ISO common name: Thiamethoxam, [redacted].
7. Test method	OECD 401 ≅ EEC B.1 ≅ FIFRA § 81-1 Deviations - none, other than the highest dose employed was 6000 mg/kg instead of 2000 mg/kg.
8 GLP	Yes (laboratory certified by the Japanese Ministry of Agriculture, Forestry and Fisheries, Tokyo, Japan)

Material and methods: Thiamethoxam (batch no. [redacted][1]) suspended in aqueous 0.5% methylcellulose solution was administered once, by gavage at a treatment volume of 20ml/kg, to groups of 5 male and 5 female fasted Sprague-Dawley SPF rats (Crj:CD strain, [redacted].) at dose levels of 0 (vehicle control), 900, 1500, 2300, 3800 and 6000mg/kg bw. The animals were checked twice daily for mortality and clinical signs, and body weights were recorded pre-dose and on days 1, 2, 3, 7, 10 and 14. Animals were maintained under observation for 14 days. Animals dying during the observation period and all survivors were submitted for necropsy and *post mortem* examination. The LD_{50} and 95% confidence limits were determined by the probit method.

Findings: Deaths were observed in both sexes at dose levels ≥1500mg/kg bw occurring between 2 and 6 hours after dosing (see Table below). In most instances, tonic convulsions preceded death. Ptosis occurred in all treated groups one hour after dosing and survivors of both sexes treated at ≥1500mg/kg bw showed reduced locomotor activity on the day of treatment. The surviving animals returned to normal on the day following treatment. Survivors showed body weight loss or retarded weight gain for 2 days after dosing. Thereafter, body weight gain was normal. Necropsy and *post mortem* examination did not reveal any treatment-related abnormalities in the animals that died, or in survivors.

1 For details regarding the purity and by-products of the test article see Document J

Table: Acute oral toxicity of thiamethoxam

Males			Females		
Dose (mg/kg)	Deaths/tested	Time of death	Dose (mg/kg)	Deaths/tested	Time of death
0	0/5	-	0	0/5	-
900	0/5	-	900	0/5	-
1500	3/5	2h (1), 4h (2)	1500	3/5	4h (2), 6h (1)
2300	4/5	2h (1), 4h (3)	2300	4/5	2h (1), 4h (3)
3800	5/5	2h (3), 4h (2)	3800	5/5	2h (3), 4h (2)
6000	5/5	2h (2), 4h (3)	6000	5/5	2h (3), 4h (2)

Conclusion: The acute oral LD_{50} of thiamethoxam in rats is 1563mg/kg bw (95% confidence limits 1267 - 1905mg/kg) in both sexes. There is no sex difference in response.

Evaluation by Competent Authorities

EVALUATION BY RAPPORTEUR MEMBER STATE

Date February 2005

Materials and Methods [redacted]

Results and discussion [redacted]

Conclusion [redacted]

Reliability [redacted]

Acceptability [redacted]

Remarks

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

1. Annex point(s)	**IIA, 5.2.1 Acute toxicity - oral**
2. Reference point (location) in dossier	Volume 7, Section 3, Annex IIA, point 5.2.1 / 02
3. Authors (year) Title Owner, Date	[redacted] An acute oral toxicity study of CGA 293'343 tech. in mice. Syngenta Crop Protection AG, unpublished report No. B-3122, CG 952058, May 23, 1996
4. Testing facility	[redacted]
5. Dates of work	October 18, 1995 - November 1, 1995
6. Test substance	ISO common name: Thiamethoxam; [redacted]
7. Test method	OECD 401 ≅ EEC B.1 ≅ FIFRA § 81-1 Deviations - none.
8. GLP	Yes (laboratory certified by the Japanese Ministry of Agriculture, Forestry and Fisheries, Tokyo, Japan)

Material and methods: Thiamethoxam (batch no. [redacted] %) suspended in aqueous 0.5% methylcellulose solution was administered once, by gavage at a treatment volume of 20ml/kg, to groups of 5 male and 5 female fasted SPF mice (Crj:CD1(ICR) strain, [redacted].) at dose levels of 0 (vehicle control), 500, 700, 1000, 1400 and 2000mg/kg bw. The animals were checked twice daily for mortality and clinical signs, and body weights were recorded pre-dose and on days 1, 2, 3, 7, 10 and 14. Animals were maintained under observation for 14 days. Animals dying during the observation period and all survivors were submitted for necropsy and *post mortem* examination. The LD_{50} and 95% confidence limits were determined by the probit method.

Findings: Deaths occurred in both sexes at dose levels ≥700mg/kg, between 15 minutes and 24 hours after dosing (see Table below). Reduced locomotor activity or prostration occurred in all thiamethoxam-treated animals within 5 - 15 minutes of treatment and clonic convulsions occurred 15 minutes to 4 hours after treatment. Survivors returned to normal appearance on the day following treatment. The body weight development of all male treated groups was unaffected throughout the observation period but the body weight gain of all female treated groups was slightly reduced on the day following dosing. Thereafter, body weight development of female groups returned to normal. Necropsy and *post mortem* examination did not reveal any treatment-related abnormalities in the animals that died, or in survivors.

Table: Acute oral toxicity of thiamethoxam

Males			Females		
Dose (mg/kg)	Deaths/treated	Time of death	Dose (mg/kg)	Deaths/treated	Time of death
0	0/5	-	0	0/5	-
500	0/5	-	500	0/5	-
700	2/5	6hours - 1 day	700	1/5	4hours
1000	4/5	1 hour - 1 day	1000	3/5	2 - 6 hours
1400	5/5	1 - 6 hours	1400	4/5	1 - 4 hours
2000	5/5	15min - 2 hours	2000	5/5	15min - 2 hours

Conclusion: The acute oral LD_{50} of thiamethoxam in mice is 783mg/kg (95% confidence limits 619 - 1000mg/kg) in males and 964mg/kg (729 - 1271mg/kg) in females, and 871mg/kg (735 - 1028mg/kg) in both sexes combined.

Evaluation by Competent Authorities

EVALUATION BY RAPPORTEUR MEMBER STATE

Date February 2005

Materials and Methods [redacted]

Results and discussion [redacted]

Conclusion [redacted]

Reliability [redacted]

Acceptability [redacted]

Remarks [redacted]

98/8 Doc IIIA section No.	6.1.1 / 03 Acute toxicity – Oral
91/414 Annex II Point addressed	5.8.1 / 01 Other toxicological studies - Toxicity studies of metabolites as referred to in the introduction point (vii)

1. Annex point(s)	IIA, 5.8.1 Other toxicological studies - Toxicity studies of metabolites as referred to in the introduction point (vii)
2. Reference point (location) in dossier	Volume 7, Section 3, Annex IIA, point 5.8.1 / 01
3. Authors (year) Title Owner, Date	[redacted] CGA 322'704 tech. (Metabolite of CGA 293'343) - Acute oral toxicity in the rat. Syngenta Crop Protection AG, unpublished report No. 982001, April 28, 1998
4. Testing facility	[redacted]
5. Dates of work	January 20, 1998 - February 17, 1998
6. Test substance	CGA 322'704 tech., [redacted]
7. Test method	OECD 401 ≅ EEC B.1 Deviations - none
8. GLP	Yes (laboratory certified by the Eidgenössisches Department des Inneren (Federal Department of Home Affairs), Bern, Switzerland)

Material and methods: CGA 322'704 tech. (batch no. [redacted] suspended in 0.5% methylcellulose solution (in aqueous 0.1% polysorbate 80), was administered once, by gavage at a treatment volume of 10ml/kg, to groups of 5 male and 5 female fasted Wistar albino rats (HanIbm:WIST strain, [redacted] at dose levels of 0 (vehicle control), 1500 and 2000mg/kg bw. The animals were checked twice daily for mortality. They were checked for clinical signs at 1, 3 and 5 hours after dosing, and then daily for the duration of the observation period. Body weights were recorded pre-dose and on days 7 and 14. Animals were maintained under observation for 14 days.

Findings: There were no deaths during the study. Tremor, piloerection and hunched posture were observed in all animals in the 2000mg/kg groups on the day of treatment, but all animals appeared normal by Day 1. No remarkable clinical observations were seen among animals in the 0mg/kg and 1500mg/kg groups. Body weights and body weight changes of animals in all groups were not affected by treatment. Necropsy examinations did not reveal any treatment-related abnormalities.

Conclusion: The acute oral LD_{50} of CGA 322'704 tech. in rats was found to be greater than 2000mg/kg bw in each sex and in both sexes combined.

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	February 2005
Materials and Methods	[redacted]

	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	

98/8 section No.	**Doc IIIA**	**6.1.1 / 04**	**Acute toxicity – Oral**
91/414 Point addressed	**Annex II**	**5.8.2 / 02**	Toxicity of metabolites

1. Annex point(s)	**IIA, 5.8.1 Other toxicological studies - Toxicity studies of metabolites as referred to in the introduction point (vii)**
2. Reference point (location) in dossier	Volume 7, Section 3, Annex IIA, point 5.8.1 / 02
3. Authors (year) **Title** **Owner, Date**	[redacted] NOA 407'475 tech. (Metabolite of CGA 293'343) - Acute oral toxicity in the rat. Syngenta Crop Protection AG, unpublished report No. 982013, April 28, 1998
4. Testing facility	[redacted]
5. Dates of work	February 25, 1998 - April 13, 1998
6. Test substance	NOA 407'475 tech., [redacted]
7. Test method	OECD 401 ≅ EEC B.1 Deviations - none
8. GLP	Yes (laboratory certified by the Eidgenössisches Department des Inneren (Federal Department of Home Affairs), Bern, Switzerland)

Material and methods: NOA 407'475 tech. (batch no. [redacted]) suspended in 0.5% methylcellulose solution (in aqueous 0.1% polysorbate 80), was administered once, by gavage at a treatment volume of 10ml/kg, to groups of 5 male and 5 female fasted Wistar albino rats (HanIbm:WIST strain, [redacted]) at dose levels of 0 (vehicle control), 500, 1000 and 1500mg/kg bw. The animals were checked twice daily for mortality. Clinical signs were recorded at 1, 3 and 5 hours after dosing, and then daily for the duration of the observation period. Body weights were recorded pre-dose and on days 7 and 14. Animals were maintained under observation for 14 days. Animals dying during the observation period and all survivors were submitted for necropsy and *post mortem* examination.

Findings: All animals in the 1500mg/kg dose groups and two males and four females in the 1000mg/kg groups were found dead on the day of treatment. One male in the 1000mg/kg group was found dead the day after application (Table 1). Ventral recumbency, hypoactivity, tremor and ataxia were seen in all animals in the 1000mg/kg groups, piloerection was observed in 3 males and 1 female in the 1000mg/kg groups, and hunched posture was seen in 2 males and 1 female in the 1000mg/kg groups. Both surviving males fully recovered within 3 days, the surviving females within 7 days. No clinical signs were seen in animals in the 0mg/kg and 500mg/kg groups. All animals of the high dose groups died before the first recording of clinical observations could be made. Body weights and body weight changes were not affected by treatment. Necropsy and *post mortem* examination did not reveal any treatment-related abnormalities in the animals that died, or in survivors.

Table 1: Acute oral toxicity of NOA 407'475 tech.

Males			Females		
Dose (mg/kg)	Deaths/tested	Time of death	Dose (mg/kg)	Deaths/tested	Time of death
0	0/5	-	0	0/5	-
500	0/5	-	500	0/5	-
1000	3/5	3h (2), 1d (1)	1000	4/5	3h (4)
1500	5/5	1h (5)	1500	5/5	1h (5)

Conclusion: The acute oral LD_{50} of NOA 407'475 tech. in rats was found to be greater than 500mg/kg bw, but lower than 1000mg/kg bw in each sex and in both sexes combined.

Evaluation by Competent Authorities

EVALUATION BY RAPPORTEUR MEMBER STATE

Date February 2005

Materials and Methods [redacted]

Results and discussion [redacted]

Conclusion [redacted]

Reliability [redacted]

Acceptability [redacted]

Remarks

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

1. Annex point(s)	**IIA, 5.2.2 Acute toxicity - percutaneous**
2. Reference point (location) in dossier	Volume 7, Section 3, Annex IIA, point 5.2.2/01
3. Authors (year) Title Owner, Date	[redacted] An acute dermal toxicity study of CGA 293'343 tech. in rats. Syngenta Crop Protection AG, unpublished report No. B-3121, CG 942112, May 23, 1996
4. Testing facility	[redacted]
5. Dates of work	October 17, 1995 - October 31, 1995
6. Test substance	ISO common name: Thiamethoxam; [redacted]
7. Test method	OECD 402 ≅ EEC B.3 ≅ FIFRA § 81-2 Deviations - none
8. GLP	Yes (laboratory certified by the Japanese Ministry of Agriculture, Forestry and Fisheries, Tokyo, Japan)

Material and methods: Thiamethoxam (batch no. [redacted][1]) formulated as a paste in distilled water was applied once for 24 hours under occlusive dressing, to the shaved dorsal skin, to groups of 5 male and 5 female Sprague-Dawley SPF rats (Crj:CD strain, [redacted].) at dose levels of 0 (vehicle control) or 2000mg/kg bw. The animals were checked twice daily for mortality and clinical signs, and body weights were recorded pre-dose and on days 1, 2, 3, 7, 10 and 14. Animals were maintained under observation for 14 days. All animals were submitted for necropsy and *post mortem* examination.

Findings: No deaths occurred and there were no clinical signs of an adverse reaction to treatment either systemic, or locally at the sites of application. Body weight development was unaffected by the application of thiamethoxam: a slight body weight loss or reduced weight gain occurred the day following application in both treated and vehicle control groups. Necropsy and *post mortem* examination did not reveal any treatment-related abnormalities in the animals that died, or in survivors.

Conclusion: The dermal LD_{50} of thiamethoxam in rats is greater than 2000 mg/kg.

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	February 2005
Materials and Methods	[redacted]

	[redacted]
Results and discussion	[redacted]
	[redacted]
	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	

98/8 Doc IIIA section No.	**6.1.3 / 01 Acute toxicity – Inhalation**
91/414 Annex II Point addressed	**5.2.3 / 01** Acute toxicity - inhalation

1. Annex point(s)	**IIA, 5.2.3 Acute toxicity - inhalation**
2. Reference point (location) in dossier	Volume 7, Section 3, Annex IIA, point 5.2.3/01
3. Authors (year) Title Owner, Date	[redacted] CGA 293'343 Tech.: Acute inhalation toxicity study in rats. Syngenta Crop Protection AG, unpublished report No. IET 95-0120, CG 942122, August 14, 1996.
4. Testing facility	[redacted]
5. Dates of work	April 17, 1996 - May 02, 1996
6. Test substance	ISO common name: Thiamethoxam; [redacted]
7. Test method	OECD 403 ≅ EEC B.2 ≅ FIFRA § 81-1 ≅ JMAFF 4200 Deviations - none, except that the limit concentration employed was less than the specified limit concentration of 5 g/m^3, since 3.72 g/m^3 was the highest technically achievable concentration with a particle size of approx. 5 µm (MMAD of 5.6 µm).
8. GLP	Yes (laboratory certified by the Japanese Ministry of Agriculture, Forestry and Fisheries, Tokyo, Japan)

Material and methods: Groups of 5 male and 5 female Sprague-Dawley SPF rats (Crj:CD strain, [redacted].) were exposed for 4 hours by inhalation, in nose-only chambers, to atmospheres of thiamethoxam (batch no. [redacted]) as pulverised dusts in air at nominal concentrations of 10.9 and 56.6g/m^3 (equivalent to mean actual concentrations of 1.02 and 3.72g/m^3). Exposure parameters are shown in Table 5.2.3-1. Animals were observed during and following exposure and thereafter for 14 days for mortality and clinical signs. Body weights were recorded weekly. After a 14-day observation period all animals were submitted for necropsy and *post mortem* examination.

Table 5.2.3-1: Exposure parameters

Parameter	Low dose	High dose
Chamber volume	32 L	32 L
Flow rate (whole system)	20 L/min	20 L/min
Nominal concentration	10.9 g/m^3	56.6 g/m^3
Analytical concentration	1.02 ± 0.05 g/m^3	3.72 ± 0.73 g/m^3
Particle size: MMAD ± SD	5.1 µm ± 0.3 µm	5.6 µm ± 0.1 µm
Particles <7.07 µm (% w/w)	67.5% at 1.02 g/m^3	66.9% at 3.72 g/m^3

MMAD : Mass median aerodynamic diameter

Findings: No deaths occurred and no treatment-related clinical signs of an adverse reaction to treatment were apparent. Soiled fur in the nasorostral region was observed to a slight degree in all animals of both groups but this is considered to be procedure-related rather than test article-related. This finding was no longer evident on post-exposure day 1 in the low dose group and by day 3 in the high dose group. Body weight gains were not affected by treatment with the exception of 2 females in the high dose group that exhibited slight decreases in body weight on day 7. Body weight recovery had occurred by day 14. Necropsy and *post mortem* examination did not reveal any treatment-related abnormalities.

Conclusion: The 4-hour inhalation LC_{50} of thiamethoxam in male and female Sprague-Dawley rats is >3.72g/m³. Higher concentrations in the respirable range are not technically feasible, and since neither clinical signs of toxicity nor deaths occurred at the highest technically achievable concentration, it is likely that the actual LC_{50} value is considerably higher.

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	February 2005
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	

98/8 Doc IIIA section No.	**6.1.4 / 01 Acute toxicity – Skin and eye irritation**
91/414 Annex II Point addressed	5.2.4 / 01 Acute toxicity - skin irritation

1. Annex point(s)	**IIA, 5.2.4 Acute toxicity - skin irritation**
2. Reference point (location) in dossier	Volume 7, Section 3, Annex IIA, point 5.2.4/01
3. Authors (year) Title Owner, Date	[redacted] A primary skin irritation study of CGA 293'343 tech. in rabbits. Syngenta Crop Protection AG, unpublished report No. B-3124, CG 942113, May 31, 1996
4. Testing facility	[redacted]
5. Dates of work	November 08, 1995 - November 11, 1995
6. Test substance	ISO common name: Thiamethoxam; [redacted]
7. Test method	OECD 404 ≅ EEC B.4 ≅ FIFRA § 81-5 ≅ JMAFF 4200 Deviations - Six instead of 3 rabbits were used - a regulatory requirement in the U.S.A.
9. GLP	Yes (laboratory certified by the Japanese Ministry of Agriculture, Forestry and Fisheries Tokyo, Japan)

Materials and methods: 0.5g thiamethoxam powder (batch no. [redacted] was applied on a lint dressing once for 4 hours, under semi-occlusive dressing, to shaved dorsal flank skin (2.5 x 2.5cm), of a group of 6 restrained, female Japanese White rabbits ([redacted].). The contra-lateral shaved flank, prepared in a similar manner but without application of test article, served as the reference site. The animals were checked daily for mortality and clinical signs. Skin reactions were evaluated 1, 24, 48 and 72 hours after removal of the patches. Dermal irritation was graded according to the Draize scoring method and the primary irritation index calculated.

Findings: All animals survived and no clinical signs were observed in any of the test animals. No irritant dermal reactions were noted in any of the animals and, therefore, the primary irritation index is zero.

Conclusion: It is concluded that thiamethoxam is not irritating to skin under the conditions of the study.

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	February 2005
Materials and Methods	[redacted]

Results and discussion	[redacted] [redacted] [redacted] were noted in any of the animals. The primary irritation index is zero.
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	

98/8 Doc IIIA section No.	**6.1.4 / 02 Acute toxicity – Skin and eye irritation**
91/414 Annex II Point addressed	**5.2.5 / 01** Acute toxicity - eye irritation

1. Annex point(s)	**IIA, 5.2.5 Acute toxicity - eye irritation**
2. Reference point (location) in dossier	Volume 7, Section 3, Annex IIA, point 5.2.5/01
3. Authors (year) Title Owner, Date	[redacted] A primary eye irritation study of CGA 293'343 tech. in rabbits. Syngenta Crop Protection AG, unpublished report No. B-3123, CG 942114, May 31, 1996
4. Testing facility	[redacted]
5. Dates of work	November 07, 1995 - November 10, 1995
6. Test substance	ISO common name: Thiamethoxam; [redacted]
7. Test method	OECD 405 ≅ EEC B.5 ≅ FIFRA § 81-4 ≅ JMAFF 4200 Deviations - Nine instead of 3 rabbits were used; the eyes of six rabbits remained unwashed (regulatory requirement in U.S.A.); the eyes of the remaining 3 animals were washed 30 seconds after instillation of the test article.
9. GLP	Yes (laboratory certified by the Japanese Ministry of Agriculture, Forestry and Fisheries, Tokyo, Japan)

Materials and methods: 0.1g thiamethoxam powder (batch no. [redacted]) was placed into the left conjunctival sac, of a group of 9 restrained, female Japanese White rabbits [redacted].). The right eye served as a control. After 2 - 3 minutes, both eyes of 3 animals (= washed) were irrigated with about 200ml physiological saline. The animals were checked daily for mortality and clinical signs. Ocular reactions were evaluated, using an ophthalmoscope, according to the Draize classification 1, 24, 48 and 72 hours after instillation. Twenty-four hours after application, a drop of 2% fluorescein sodium solution was instilled into the eyes and immediately rinsed with water in order to assist with visualisation of corneal damage.

Findings: All animals survived and no clinical signs were observed in any of the test animals. Minimal (grade 1) erythema and oedema of the conjunctivae occurred at 1 hour in the unwashed eye of all animals and in the washed eye of 2/3 animals. The other animal in the washed group developed minimal conjunctival oedema only. Transient eye closure and discharge were observed in all animals immediately after application. No signs of eye irritation were present at 24, 48, and 72 hours in unwashed and washed eyes (see Table below).

Table: Eye irritation scores according to Draize scheme - unwashed and washed eyes

Observation	Time	Unwashed group						Washed group		
		1101	1102	1103	1104	1105	1106	2101	2102	2103
Cornea:	1 hour	0	0	0	0	0	0	0	0	0
	24 hours	0	0	0	0	0	0	0	0	0
	48 hours	0	0	0	0	0	0	0	0	0
	72 hours	0	0	0	0	0	0	0	0	0
	24 to 72 h	mean = 0								
Iris:	1 hour	0	0	0	0	0	0	0	0	0
	24 hours	0	0	0	0	0	0	0	0	0
	48 hours	0	0	0	0	0	0	0	0	0
	72 hours	0	0	0	0	0	0	0	0	0
	24 to 72 h	mean = 0								
Conjunctival redness:	1 hour	1	1	1	1	1	1	1	0	1
	24 hours	0	0	0	0	0	0	0	0	0
	48 hours	0	0	0	0	0	0	0	0	0
	72 hours	0	0	0	0	0	0	0	0	0
	24 to 72 h	mean = 0								
Conjunctival oedema:	1 hour	1	1	1	1	1	1	1	1	1
	24 hours	0	0	0	0	0	0	0	0	0
	48 hours	0	0	0	0	0	0	0	0	0
	72 hours	0	0	0	0	0	0	0	0	0
	24 to 72 h	mean = 0								

Conclusion: Based on the mean eye irritation scores 24 - 72 hours after instillation, it is concluded that thiamethoxam is not irritating to eyes under the conditions of the study.

Evaluation by Competent Authorities

EVALUATION BY RAPPORTEUR MEMBER STATE

Date February 2005

Materials and Methods [redacted]

Results and discussion [redacted]

Conclusion [redacted]

Reliability [redacted]

Acceptability [redacted]

Remarks

98/8 Doc IIIA section No.	**6.1.5 / 01 Acute toxicity – Skin sensitisation**
91/414 Annex II Point addressed	**5.2.6 / 01** Acute toxicity - skin sensitisation

1. Annex point(s)	**IIA, 5.2.6 Acute toxicity - Skin sensitization**
2. Reference point (location) in dossier	Volume 7, Section 3, Annex IIA, point 5.2.6/01
3. Authors (year) Title Owner, Date	[redacted] CGA 293'343 tech. - skin sensitisation test in the guinea pig - maximization test. Syngenta Crop Protection AG, unpublished report No. 942115, December 21, 1995.
4. Testing facility	[redacted]
5. Dates of work	October 16, 1995 - November 9, 1995
6. Test substance	ISO common name: Thiamethoxam; [redacted]
7. Test method	OECD 406 ≅ EEC B.6 ≅ JMAFF Deviations - To comply with Japanese guidelines and requirements, the following deviations from the standard protocol were necessary: Each group consisted of 20 animals (10 males and 10 females). A concurrent positive control group treated with mercaptobenzothiazole (MBT) was included in this test. The test pattern (cranial to caudal sequence in duplicate) was as follows: Test group: Test article/test article + adjuvant/adjuvant Negative controls: Adjuvant/adjuvant + vehicle/vehicle Positive controls: MBT/MBT + adjuvant/adjuvant
8. GLP	Yes (laboratory certified by the Eidgenössisches Departement des Inneren (Federal Department of Home Affairs), Bern, Switzerland)

Materials and methods: In the main study, thiamethoxam (batch no. [redacted] was administered to groups of 10 male and 10 female Pirbright White guinea pigs (Tif:DHP strain, [redacted]). Following completion of intradermal and topical range-finding studies, 3 groups of animals received 0.1 ml intradermal injections of 1% thiamethoxam in peanut oil, 1% thiamethoxam in adjuvant/saline and adjuvant/saline alone (test group), or 0.5% MBT (mercaptobenzothiazole) in peanut oil, 0.5% MBT in adjuvant/saline and adjuvant/saline alone (positive control), or peanut oil alone, adjuvant/saline mixture and adjuvant/saline mixture with peanut oil (negative control). One week later the groups were treated topically under occlusive dressing for 48 hours with 30% thiamethoxam in vaseline, 50% MBT in vaseline or vaseline alone (respectively). Two weeks later the groups were challenged topically under occlusive dressing for 24 hours with 10% thiamethoxam in vaseline (test and negative control groups) or 10% MBT in vaseline. Challenge reactions were scored according to the Draize scale 24 and 48 hours after removal of the dressings.

Findings: A skin reaction (erythema reaction with Draize score 1) was observed in one male (corresponding to a reaction rate of 5%) from the test group animals after 48 hours only. No irritant skin reactions occurred in the negative control group. In contrast, the positive control group showed positive reactions (Draize score 1-3) in 17/20

animals after 24 and 48 hours, corresponding to a sensitisation rate of 85%. (see Table below). No effect on body weights occurred during the experimental period.

Table: Number of animals with signs of allergic skin reactions (erythema or oedema)

	5.5.1.1.1.1 TEST GROUP		Negative control group		Positive control group	
Scored after	24 h	48 h	24 h	48 h	24 h	48 h
Erythema reactions:						
Vehicle control	0/20	0/20	0/20	0/20	2/20	3/20
Test article	0/20	1/20	0/20	0/20	17/20	17*/20
Oedema reactions:						
Vehicle control	0/20	0/20	0/20	0/20	1/20	0/20
Test article	0/20	0/20	0/20	0/20	16/20	13/20

* With scaling

Conclusion: Based on a skin reaction incidence of 5%, which is below the 30% threshold of significance specified in Commission Directive 93/21/EEC, thiamethoxam is non-sensitising and no classification is required.

Evaluation by Competent Authorities

EVALUATION BY RAPPORTEUR MEMBER STATE

Date February 2005

Materials and Methods [redacted]

Results and discussion [redacted]

Conclusion [redacted]

Reliability [redacted]

Acceptability [redacted]

Remarks

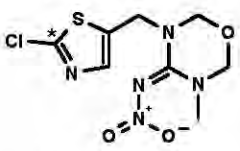
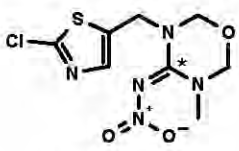
98/8 Doc IIIA section No.	**6.2 / 01**	**Metabolism studies in mammals. Basic toxicokinetics, including a dermal absorption study**
91/414 Annex Point addressed	**II 5.1.1 / 01**	**Absorption, distribution and excretion in rats**

1. Annex point(s)	**IIA, 5.1.1 Studies on absorption, distribution, excretion and metabolism in mammals - Absorption, distribution, and excretion in rats**
2. Reference point (location) in dossier	Volume 7, Section 3, Annex IIA, point 5.1.1/01
3. Authors (year) **Title** **Owner, Date**	[redacted] Absorption, Distribution, and Excretion of [Thiazol-2-^{14}C] and [Oxadiazin-4-^{14}C] CGA 293'343 in the Rat. Syngenta Crop Protection AG, unpublished report No. 027AM01, PR 11/96, August 15, 1996
4. Testing facility	[redacted]
5. Dates of work	April 05, 1996 - May 07, 1996
6. Test substance	ISO common name: Thiamethoxam *Non-labeled compound:* [redacted] [*Thiazol-2-^{14}C*] - *labeled compound:* [redacted] [*Oxadiazin-4-^{14}C*] - *labeled compound:* Batch numbers.: [redacted]
7. Test method	OECD 417 ≡ FIFRA § 85-1 ≡ Japan MAFF ≡ 94/79/EEC Deviations - none
8. GLP	Yes (laboratory certified by the Eidgenössisches Departement des Inneren (Federal Department of Home Affairs), Bern, Switzerland)

Material and methods:

Test material: Thiamethoxam (CGA 293'343)

Radiolabelled compounds:

	[Thiazol-2-^{14}C]		[Oxadiazin-4-^{14}C]	
Structure	 * = ^{14}C position		 * = ^{14}C position	
Batch:	[redacted]		[redacted]	
Specific activity:	2550 (68.9 µCi/mg)	kBq/mg	2120 (57.3 µCi/mg)	kBq/mg
	3220 kBq/mg (87.0 µCi/mg)		3130 kBq/mg (84.6 µCi/mg)	
Radiochemical purity:	[redacted]		[redacted]	

Non-radiolabelled compounds:

Batch:	KI-4654-18	AMS 780/101
Purity:	> 98 %	> 99 %

Vehicle: mixture of polyethylene glycol 200/ethanol 5/3 (v/v).

Doses and administration: Two nominal dose levels of 0.5 and 100 mg/kg body weight were used. Each animal received about 0.8 ml of the respective administration solution by stomach tube, except the animals of Groups G1, G3 (0.9 ml) and F2, F6 (1.0 ml). For the pre-treatment period the animals of Group C1 received the respective amount of non-radiolabelled test substance dissolved in 0.7 - 0.8 ml of the vehicle. For the intravenous administration (Group A1) the test substance was dissolved in physiological saline (0.9% NaCl). Each animal received about 0.3 ml of the administration solution by syringe into the tail vein.

Animals: Young, adult male and female rats Tif: RAIf (SPF) were used.

Sampling: Urine, faeces, bile, and expired air were individually and separately collected. For the blood kinetics (Group A1, B1, B2, D1, D2) blood was taken from three animals of each group and each sex by amputating the tip of the tail.

Table: Kinetics in the rat - experimental scheme

Group	**Animals**	**Dose (nominal)**	**Administration and sampling**
A1	4 males 5 females	0.5 mg/kg [Thiazol-2-^{14}C] 229 kBq (6.2 µCi)	Single intravenous dose. Urine: 0 - 8, 8 - 24, 24 - 48, 48 - 72, 72 - 96, 96 - 120, 120 - 144, 144 - 168 h. Faeces: 0 - 24, 24 - 48, 48 - 72, 72 - 96, 96 - 120, 120 - 144, 144 - 168 h. Blood: ¼, ½, 1, 2, 4, 8, 24, and 48 hours after dosing. Tissues: Seven days after dosing the animals were killed and the remaining carcass was saved for radiometry.
B1	5 males 5 females	0.5 mg/kg [Thiazol-2-^{14}C] 278 kBq (7.5 µCi)	Single oral dose. Sample collection as in Group A1. Additionally the blood was collected 12 hours after dosing. Tissues: Seven days after dosing the animals were killed and the following tissues and organs taken and weighed prior to analysis: bone, brain, fat (abdominal), gonads (testes/ovaries), heart, kidneys, liver, lungs, plasma, skeletal muscle, spleen, uterus, whole blood, residual carcass.
B2	5 males 5 females	0.5 mg/kg [Oxadiazin-4-^{14}C] 288 kBq (7.8 µCi)	Single oral dose. Sample collection as in Group B1.
C1	5 males 5 females	0.5 mg/kg [Thiazol-2-^{14}C] 205 kBq (5.6 µCi)	Single oral dose of [Thiazol-2-^{14}C] CGA 293'343 preceded by 14 daily doses of about 0.5 mg/kg non-radiolabelled CGA 293'343. Sample collection as in Group B1.
D1	5 males 5 females	100 mg/kg [Thiazol-2-^{14}C] 6590 kBq (178 µCi)	Single oral dose. Sample collection as in Group B1. Additionally the expired air was absorbed and collected: 0 - 24, 24 - 48 h.
D2	5 males 5 females	100 mg/kg [Oxadiazin-4-^{14}C] 6422 kBq (174 µCi)	Single oral dose. Sample collection as in Group D1.
F1	12 males	0.5 mg/kg [Thiazol-2-^{14}C] 230 kBq (6.2 µCi)	Single oral dose. Tissues as listed for Group B1 were taken at 4 time points, i.e. t_{cmax}, $t_{cmax/2}$, and two additional time points based on the blood kinetics as determined in the corresponding Group B1. Time points: 2, 8, 12, 24 h after dosing.
F2	12 males	100 mg/kg [Thiazol-2-^{14}C] 2464 kBq (67 µCi)	Single oral dose. Tissues as listed for Group B1 were taken at 4 time points, i.e. t_{cmax}, $t_{cmax/2}$, and two additional time points based on the blood kinetics as determined in the corresponding Group D1. Time points: 2, 7, 12, 24 h after dosing.
F3	12 males	0.5 mg/kg	Single oral dose.