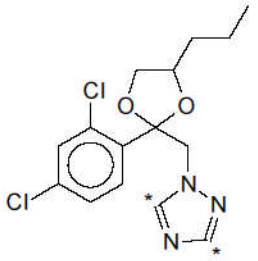
	Structural formula: (position of label)	[U-^{14}C-triazole]CGA 64250



* = 14C

4.2	**Specification**	[redacted]
4.3	**Storage stability**	Not applicable
4.4	**Stability in vehicle**	Not applicable
4.5	**Homogeneity in vehicle**	Not applicable
4.6	**Validity**	Not applicable
5	**Vehicle / solvent**	Stock solution in acetone adsorbed onto ground corn cobs in gelatin capsules
6	**Physical form**	See 5
7.1	**Test method**	In house method. Guidelines were not available at the time the test was performed.
7.2	**Justification**	Report was accepted by several European Authorities and by EPA
7.3	**Copy of method**	Description of the test method is included in the report
8	**Choice of method**	Not applicable
9	**Deviations**	Not applicable
10.1	**Certified laboratory**	Not applicable
10.2	**Certifying authority**	Not applicable
10.3	**GLP**	No
10.4	**Justification**	When the study was performed, GLP was not required
11.1	**GEP**	Not applicable
11.2	**Type of facility (official or officially recognized)**	[redacted]
11.3	**Justification**	Not applicable

12	**Test system**	**Test species**:	laying hens (strain: Leghorn)
		Source:	[redacted]
		Age/weight (at time of dosing):	1.58 kg and 1.68 kg
		Application	oral application
		Dose levels:	on 16 consecutive days 1 application with [Phenyl-^{14}C]CGA 64250/hen1 or [Triazole-^{14}C]CGA 64250/hen2 equivalent to 54.2 ppm and 48.0 ppm in feed, respectively
		vehicles or solvents used/concentration:	stock solution in acetone adsorbed onto ground corn cobs in gelatin capsules, 5.49 mg and 5.99 mg ^{14}C CGA 64250 / capsule, respectively
		Group size:	one hen per label

Analytical methods:	The hens were acclimatized for 6 days prior to dosing. Excreta and eggs were collected daily and the eggs were separated into yolks and whites. About 24 hours after the last dose the hens were sacrificed and blood and tissue samples were collected as follows: liver, kidney, muscle, skin and fat. Quantitation of the radioactivity in tissues and extracts was by combustion with subsequent LSC-measurement or direct LSC-measurement, respectively.
Radioactive areas on plates:	Not applicable
Non-radioactive standards:	Not used
Radioassay:	Liquid scintillation counting

13 Findings

At [redacted], two chickens were orally dosed--one with phenyl- and one with triazole-^{14}C labeled propiconazole--for 16 consecutive days at 54.2 ppm and 48.0 ppm, respectively. The chickens were sacrificed 24 hours after the last dose.

The objectives of this study were to compare metabolism of phenyl-^{14}C-propiconazole and triazole-^{14}C-propiconazole in chickens.

Most of the radioactivity [redacted] was eliminated in the excreta regardless of label.

Radioactivity levels in the egg yolk and egg white fluctuated and accounted from 0.13% to 0.36% of the total ^{14}C for both labels. Plateau in yolks and whites was reached after 11 dosings between 0.870 ppm and 1.180 ppm.

Very small portion of the radioactivity was in tissues (0.17-0.27%). Radioactive levels in tissues and blood showed label differences -- in muscle 7-fold, in skin 1.5-fold and in blood 3.5-fold higher for the triazole label than the phenyl label, indicating a cleavage between the phenyl and triazole ring.

Over 60.9% of the ^{14}C was extractable regardless of the label. The ratio of organic soluble components to aqueous soluble components varied by tissue type. Egg yolk and egg white were mainly organic soluble (55.%-77.4%) for both labels.

With the exception of fat tissue, the nonextractable components in the samples for phenyl label were higher (20.3%-40.6%) than for the triazole label (3.1%-25.1%).

14	**Statistics**	Not applicable
15 (published)	**References**	No publications cited in this summary
16 (unpublished)	**References**	No unpublished data cited in this summary
17	**Reliability Indicator**	1

Data Protection Claim	Yes

Table 1: Residual radioactivity in tissues, eggs and excreta of hens after oral administration of 48.0 ppm [U-^{14}C-triazole]CGA 64250 and 54.2 ppm [U-^{14}C-phenyl]CGA 64250 in the feed.

	[U-^{14}C-triazole]CGA 64250	[U-^{14}C-phenyl]CGA 64250

Tissue	ppm	% of Total Dose	ppm	% of Total Dose
Liver	1.587	0.060	1.823	0.060
Kidney	1.442	0.020	2.028	0.025
Br. Muscle	0.446	0.100	0.046	0.010
Th. Muscle	0.405	0.060	0.072	0.010
Br. Skin	0.226	0.010	0.169	0.010
Th. Skin	0.278	0.010	0.180	0.010
Fat	0.142	0.012	0.190	0.020
Blood	0.666	0.070	0.187	0.020
Egg Yolk		0.21		0.13
day 1	0.339		0.092	
day 5	0.601		0.514	
day 10	0.985		0.752	
day 16	0.896		0.737	
Egg White		0.36		0.20
day 1	0.684		0.276	
day 5	0.494		0.396	
day 10	0.864		0.127	
day 16	0.578		0.327	
Excreta		102.70		94.10
CO_2		not sampled		not sampled
Total		103.61		94.60

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	27.6.2005
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	[redacted]

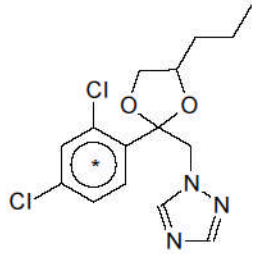
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating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

PP 2.504 / WM / 27. 10. 1994

98/8 Doc IIIA section No.	6.2/18 6.2/19	Metabolism studies in mammals. Basic toxicokinetics, including a dermal absorption study
91/414 Annex Point addressed	II 5.1.3 / 04a 5.1.3 / 04b	Biokinetics and metabolism in farm animals

1.2	Title	**Part A: Biological Report for the Metabolism of ^{14}C-Propiconazole in Laying Hens** **Part B: Metabolism of [Phenyl-^{14}C] Propiconazole in Chickens**
1.3	Report and/or project N° Syngenta File N° (SAM)	BIOL-89009 (Part A) and F-00051 (Part B) 64250/2468 (Part A) 64250/2022 (Part B)
1.4	Lab. Report N°	
1.5	91/414 Cross Reference	6.3 / 02 (A, B)
1.6	Authors	Report: [redacted] Summary: [redacted]
1.7	Date of report	January 5, 1990 (Part A) June 7, 1990 (Part B)
1.8	Published / Owner	No / Syngenta Limited
2.1	Testing facility	[redacted]
2.2	Dates of experimental work	March 29, 1989 (Application) November 30, 1989 (Completion of analytical work)
3.	Objectives	see findings

4.1	Test substance	ISO common name	Propiconazole
		Trade name	TILT
		Batch:	[redacted]
		^{14}C-labelled test substance	Yes [x] No [ ]
		Specific activity of [U-^{14}C-phenyl]CGA 64250	[redacted]
		Radiochemical purity of the test substance	[redacted]
		Structural formula: (position of label)	[U-^{14}C-phenyl]CGA 64250



* = 14C

4.2	Specification	[redacted]
4.3	Storage stability	Not applicable
4.4	Stability in vehicle	Not applicable
4.5	Homogeneity in vehicle	Not applicable
4.6	Validity	Not applicable
5	Vehicle / solvent	Stock solution adsorbed onto granular cellulose in gelatin capsules
6	Physical form	See 5

7.1	**Test method**	EPA Pesticide Assessment Guidelines, Subdivision O, 171-4
7.2	**Justification**	Reregistration of Propiconazole
7.3	**Copy of method**	Description of the test method is included in the report
8	**Choice of method**	Not applicable
9	**Deviations**	Not applicable
10.1	**Certified laboratory**	Not applicable
10.2	**Certifying authority**	Not applicable
10.3	**GLP**	Yes
10.4	**Justification**	-
11.1	**GEP**	Not applicable
11.2	**Type of facility (official or officially recognized)**	[redacted]
11.3	**Justification**	Not applicable

12	**Test system**	**Test species**:	laying hens (strain: Leghorn)
		Source:	[redacted]
		Age/weight (at time of dosing):	50 wks / 1.5 - 1.9 kg
		Application	oral application
		Dose levels:	on 8 consecutive days 1 application with [Phenyl-^{14}C]CGA 64250/hen equivalent to 67 ppm in feed
		vehicles or solvents used/concentration:	stock solution adsorbed onto granular cellulose in gelatin capsules, 10 mg ^{14}C CGA 64250 / capsule
		Group size:	four hens
		Analytical methods:	The hens were acclimatized for 16 days prior to dosing. Excreta and eggs were collected daily and the eggs were separated into yolks and whites. Six hours after the last dose the hens were sacrificed and blood and tissue samples were collected as follows: liver, kidney, lean meat, skin + fat, peritoneal fat, heart, gizzard and crop. Quantitation of the radioactivity in tissues and extracts was by combustion with subsequent LSC-measurement or direct LSC-measurement, respectively.
		Radioactive areas on plates:	Ambis Radioanalytic Imaging System
		Non-radioactive standards:	Fluorescence quenching under short wavelength ultraviolet light
		Radioassay:	Liquid scintillation counting

13 Findings

The metabolism of [Phenyl-^{14}C]propiconazole was determined utilizing the in-life facilities [redacted] (from 29 March 89 to 5 April 89). Four laying hens were dosed daily with 10 mg of ^{14}C-propiconazole (67 ppm in feed based on 150 g feed/day intake) in a gelatin capsule for 8 consecutive days. Eggs and excreta were collected during the dosing phase. Six hours after the last dose, the animals were sacrificed and tissues excised. From 73 to 87 % of administered ^{14}C-dose was found in excreta. Edible tissues were found to contain the following levels of ^{14}C-residues calculated as propiconazole: liver (3.2-5.0 ppm), kidney (3.3-

5.3 ppm), fat (0.5-0.7 ppm), and muscle (0.3-0.6 ppm). Egg ^{14}C-residues were determined in whites and yolks: egg whites (maximum of 0.70 ppm at 5 days) and egg yolks (maximum of 1.67 ppm at 7 days).

Three major metabolites were identified in poultry:

A: propiconazole

B: 1-{[2-(2,4-dichlorophenyl)-4-(2-hydroxypropyl)-1,3-dioxolan-2-yl]methyl}-1H-1,2,4-triazole

C: 1-{[2-(2,4-dichlorophenyl)-2-hydroxy]ethyl}-1H-1,2,4-triazole

Metabolites A, B and C accounted for most of the ^{14}C-residues found in tissues and eggs: liver (87%), kidney (51%), fat (87%), muscle (89%), egg white (96%) and egg yolk (88%).

14	**Statistics**	Not applicable
15 (published)	**References**	No publications cited in this summary
16 (unpublished)	**References**	No unpublished data cited in this summary
17	**Reliability Indicator**	1

Data Protection Claim	Yes

Table 1: Residual radioactivity in tissues, eggs and excreta of hens after oral administration of 67 ppm [U-^{14}C-phenyl]CGA 64250 in the feed.

	[U-^{14}C-phenyl]CGA 64250	
Tissue	ppm[1]	% of Total Dose
Liver	3.94	
Kidney	4.19	
Gizzard	2.38	
Crop	2.28	
Peritoneal Fat	0.98	
Heart	0.71	
Blood	0.69	
Skin/Fat	0.59	
Thigh Muscle	0.40	
Breast Muscle	0.33	
Egg Yolk		
day 1	0.05	
day 2	0.42	
day 3	0.91	
day 4	1.26	
day 5	1.30	
day 6	1.54	
day 7	1.67	
day 8	1.53	
Egg White		
day 1	0.15	
day 2	0.33	
day 3	0.34	
day 4	0.31	
day 5	0.70	
day 6	0.59	
day 7	0.31	
day 8	0.27	
Excreta		82.9

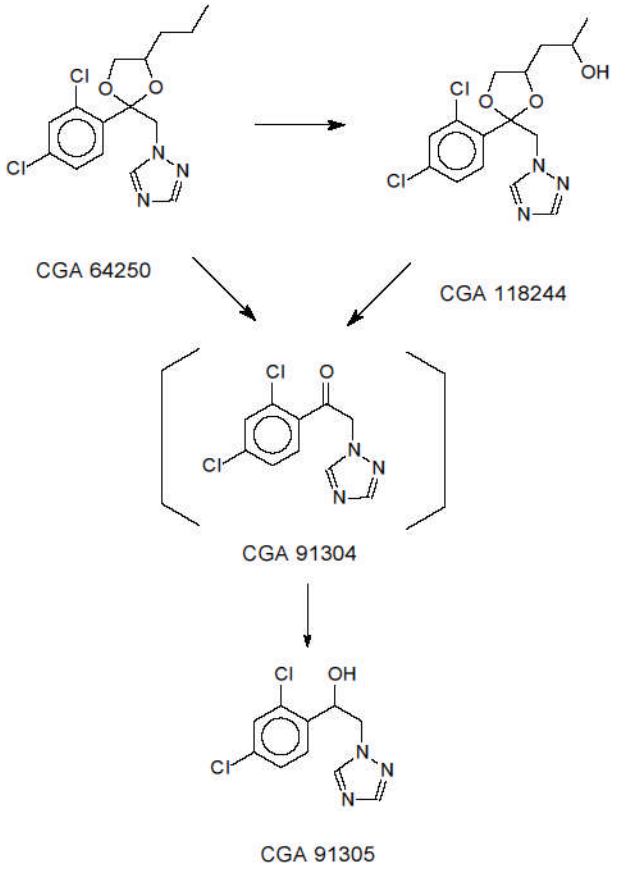
[1] as ppm propiconazole equivalents

Table 2: Summary of metabolite characterization in tissue and eggs of laying hens dosed with [U-^{14}C-phenyl]CGA 64250

Animal Parts[1]	Residues [ppm]	Acetonitrile Extract [% of total residues]				Water Extracts [%]	N.E. [%]	Recovery [%]
		total	CGA 64250	CGA 118244	CGA 91305			
Liver	3.24	73.1	1.5	3.0	59.0	12.6	17.8	103.5
Kidney	3.33	94.3	2.0	2.0	44.5	11.1	17.9	123.3
Thigh Muscle	0.32	106.2	7.5	2.0	85.0	2.5	2.3	111.0
Fat/Skin	0.56	100.3	40.0	4.0	43.0	0.5	1.8	102.6
Egg White (day 6)	0.37	103.0	28.0	52.5	18.5	-	1.8	104.8
Egg Yolk (day 6)	1.18	82.8	12.5	9.0	51.5	-	14.3	97.1

[1] Values from one animal

Figure 1: Proposed metabolic pathway for CGA 64250 in laying hens[2]



[2] Metabolites detected with the phenyl labelled propiconazole

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	27.6.2005
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	[redacted]

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

PP 2.504 / WM / 27. 10. 1994

98/8 Doc IIIA section No.	6.3.1	Repeated dose toxicity (oral)
91/414 Annex Point addressed	II 5.3.1 / 01	Short-term toxicity - oral 28-day studies

1.2	Title	CGA 64'250 techn.: 28 days cumulative toxicity study on rats
1.3	Report and/or project N° Syngenta File N° (SAM)	79 16 95 64250 / 1596
1.4	Lab. Report N°	79 16 95
1.5	91/414 Cross Reference to original study / report	5.3.1 / 01
1.6	Authors	Report: [redacted] Summary:
1.7	Date of report	November 11, 1980
1.8	Published / owner	Unpublished / Syngenta
2.1	Testing facility	[redacted]
2.2	Dates of experimental work	April 28 to June 2, 1980
3.	Objectives	Investigation of cumulative toxicity in rats
4.1	Test substance	CGA 64'250, technical grade active ingredient
x4.2	Specification	[redacted]
4.3	Storage stability	Dose solutions were freshly prepared every day before the administration
4.4	Stability in vehicle	not applicable
4.5	Homogeneity in vehicle	not applicable
4.6	Validity	not applicable
5	Vehicle / solven	2% aqueous carboxymethylcellulose
6	Physical form	viscous liquid
7.1	Test method	not specified
7.2	Justification	The study was conducted before the OECD Guideline 407 was released
7.3	Copy of method	Methodological details are part of the original report submitted under 5.3.1 / 01
8	Choice of method	not applicable
9	Deviations from EC-Directive 92/69 B7	Neurological examinations beyond normal clinical inspections were not conducted. Other, formal deviations are outlined below.
10.1	Certified laboratory	not applicable
10.2	Certifying authority	not applicable
10.3	GLP	no

10.4 Justification The study was performed before GLP regulations were enacted.

11.1 GEP not applicable

11.2 Type of facility (official or officially recognised) [redacted]

11.3 Justification not applicable

x12 Test system

Animal species: Rat, Tif RAIf (SPF)
Source: [redacted]
Dose levels: 0, 50, 150 and 450 mg/kg
Group size: 10 males and 10 females
Age/weight: Young adult (8 weeks), 211-221 g (males) and 181-191g (females)
Administration: Oral by gastric intubation
Study duration: 28 days
General study
Design: Daily treatment (10 ml/kg), 7 days per week for 4 weeks.
Mortality: Twice daily
Clinical signs: Daily
Ophthalmology: Pretest and before sacrifice in all individuals
Hearing test: Pretest and before sacrifice in all individuals
Body weight: Weekly
Food consumption: Weekly
Hematology: At the end of the treatment period (5 animals per sex and group)

Red blood cells

✓ Erythrocyte count (RBC)	✓ Mean corp. hemoglobin (MCH)
✓ Hemoglobin (Hb)	Mean corp. Hb. conc. (MCHC)
✓ Hematocrit (Hct)	Red cell vol. distr. width (RDW)
✓ Mean corp. volume (MCV)	Hb conc. distr. width (HDW)

White blood cells

✓ Total leukocyte count	✓ Lymphocytes (differential)
✓ Neutrophils (differential)	✓ Monocytes (differential)
✓ Eosinophils (differential)	Large unstained cells (diff.)
✓ Basophils (differential)	

Clotting Potential

✓ Prothrombine time	✓ Thrombocyte count

Clinical chemistry: At the end of the treatment period (5 animals per sex and group)

Electrolytes

Calcium	✓ Potassium
✓ Chloride	✓ Sodium
Phosphorus (inorganic)	

Metabolites and Proteins

✓ Albumin	✓ Globulin
✓ A/G ratio	✓ Glucose
Bilirubin (total)	✓ Protein (total)
Cholesterol	✓ Urea
Creatinine	

Enzymes:

✓ Alanine aminotransferase (ALT)	✓ Alkaline phosphatase (ALP)
✓ Aspartate aminotransferase (AST)	✓ γ-glutamyl transpeptidase (γ-GT)

Urinalysis: At the end of the treatment period (5 animals per sex and group)

Quantitative parameters:

✓ Urine volume	✓ pH-value
✓ Relative density	

Semiquantitative parameters:

✓ Bilirubin	✓ Ketones
✓ Blood	✓ Protein
✓ Color	Urobilirubin
✓ Glucose	

Pathology: The following organs were collected (column C), weighed (W) and examined histopathologically (H) from all individuals.

C	W	H		C	W	H	
✓	✓		adrenals	✓			pituitary

✓		aorta	✓		prostate
✓	✓	brain			rectum
		caecum	✓		salivary gland
✓		colon	✓		prostate
✓		duodenum			seminal vesicles
		epididymides	✓		skin
✓		esophagus	✓		spinal cord
✓		eyes	✓		spleen
		femur (with joint)	✓		sternum with bone marrow
		gross lesions	✓		stomach
✓	✓	heart	✓	✓	testis
✓		ileum	✓		thymus
✓		jejunum	✓		thyroid/parathyroid
✓	✓	kidneys	✓		trachea
		lacrymal glands	✓		urinary bladder
✓	✓ ✓	liver	✓		uterus
✓		lung			
✓		lymph nodes			*others:*
✓		mammary gland (female)			muzzle
✓		muscle, skeletal			orbital gland
✓		nerve, peripheral			tongue
✓	✓	ovary			Zymbal gland
✓		pancreas			body (exsanguinated)

x13 Findings

Mortality: Three females (2 from the top dose group and one treated at 150 mg/kg) died during the study. The deaths were not considered to be related to the treatment.

Clinical signs: The top dose group females generally showed sedation, ruffled fur and dyspnea during the first week of treatment. No symptoms were noted during later phases of the study.

Ophthalmology: No treatment-related changes.

Hearing test: No treatment-related changes.

xBody weight: A minimally reduced body weight gain was noted in the top dose group males. Differences did not attain statistical significance.

Food consumption: Minimally reduced in top dose group females. Differences did not attain statistical significance.

xHematology: Minimally reduced RBC counts and hemoglobin concentrations in the females from the top dose group. Slightly increased MCV in both sexes treated at 450 mg/kg. Minimally increased thrombocyte counts in all treated males. All changes were of insufficient manitude to be toxicologically significant.

xClinical chemistry: Minimally increased plasma glucose concentrations in all treated females, minimally increased $\alpha 2$ globulin fraction in both sexes and reduced γ globulins in the females. Higher chloride concentration in females of the top dose group. All changes were of insufficient manitude to be toxicologically significant.

xUrinalysis: The specific gravity was slightly increased in males treated at 150 and 450 mg/kg and in the females of the top dose group.

xOrgan weights: Absolute and relative liver weights were dose-relatedly increasd in all treated females and in the males treated at 150 mg/kg and above.

Pathology: A minimal to moderate hypertrophy of hepatocytes was noted in both sexes receiving 150 mg/kg CGA 64'250 and higher. In addition, focal liver necroses were diagnosed in several females from the top dose group and in one male treated at 150 mg/kg.

NOEL: Males 50 mg/kg. No NOEL reached in the females.

14 Statistics Uni-variate analysis. Comparison to controls by Lepage-test, trend analysis by the Jonckheere t-test.

15 (published) References none

16 data	**Unpublished**	none
x17 Indicator	**Reliability**	1

Data Protection Claim	Yes

Evaluation by Competent Authorities

EVALUATION BY RAPPORTEUR MEMBER STATE

Date 19.1.2005

Materials and Methods [redacted]

Results and discussion [redacted]

Conclusion [redacted]

Reliability [redacted]

Acceptability [redacted]

Remarks [redacted]

[redacted]

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

PP 2.504 / WM / 25.10.1994

98/8 Doc IIIA section No.	**6.3.2/01**	**Repeated dose toxicity (dermal)**
91/414 Annex Point addressed	**II 5.3.3 / 01**	Short-term toxicity - other routes

1.2	**Title**	CGA 64'250 techn.: 21 day percutaneous toxicity study in rabbits
1.3	**Report and/or project N° Syngenta File N° (SAM)**	79 00 07 64250 / 1595
1.4	**Lab. Report N°**	79 00 07
1.5	**91/414 Cross Reference to original study / report**	5.3.3 / 01
1.6	**Authors**	Report: [redacted] Summary:
1.7	**Date of report**	May 30, 1980
1.8	**Published / owner**	Unpublished / Syngenta
2.1	**Testing facility**	[redacted]
2.2	**Dates of experimental work**	August 13 to September 9, 1979
3.	**Objectives**	Investigation of cumulative dermal toxicity in rabbits
4.1	**Test substance**	CGA 64'250, technical grade active ingredient
x4.2	**Specification**	[redacted]
4.3	**Storage stability**	stable at room temperature
4.4	**Stability in vehicle**	not applicable
4.5	**Homogeneity in vehicle**	not applicable
4.6	**Validity**	not applicable
5	**Vehicle / solven**	The test material was applied undiluted
6	**Physical form**	viscous liquid
7.1	**Test method**	not specified
7.2	**Justification**	The study was conducted before the OECD Guideline 410 was released
7.3	**Copy of method**	Methodological details are part of the original report submitted under 5.3.3 / 01
8	**Choice of method**	not applicable
9	**Deviations from EC-Directive 92/69 B9**	The duration of treatment was 21 instead of the 28 days recommended. Doses higher than 1'000 mg/kg are not required. Testing on abraded skin is not required. Other, formal deviations are outlined below.
10.1	**Certified laboratory**	not applicable
10.2	**Certifying authority**	not applicable
10.3	**GLP**	no

10.4 **Justification** The study was performaed before GLP regulations were enacted.

11.1 **GEP** not applicable

11.2 (official or officially recognised) **Type of facility** [redacted]

11.3 **Justification** not applicable

x12 **Test system**

Animal species: Rabbit, New Zealand White
Source: [redacted]
Dose levels: 0, 200, 1'000 and 5'000 mg/kg
Group size: 10 males and 10 females
Age/weight: 2.0-2.6 kg
Administration: Dermal application to shaved skin under occlusive dressing for 6 hours to an area of 8.5 x 6.5 cm (10% of the body surface).
Study duration: 28 days
General study
Design: Daily treatment, 5 days per week for 3 weeks. In half of the animals, the skin was abraded before the start and in the middle of the study period.
Mortality: Daily
Clinical signs: Daily
Local irritation: Daily
Body weight: Weekly
Food consumption: Weekly
xHematology: At the end of the treatment period (all animals)

Red blood cells

✓ Erythrocyte count (RBC)	✓ Mean corp. hemoglobin (MCH)
✓ Hemoglobin (Hb)	✓ Heinz Bodies
✓ Hematocrit (Hct)	✓ Reticulocytes
✓ Mean corp. volume (MCV)	✓ Methemoglobin

White blood cells

✓ Total leukocyte count	✓ Lymphocytes (differential)
✓ Neutrophils (differential)	✓ Monocytes (differential)
✓ Eosinophils (differential)	Large unstained cells (diff.)
✓ Basophils (differential)	

Clotting Potential

✓ Prothrombine time	✓ Partial thromboplastin time
	✓ Thrombocyte count

xClinical chemistry: At the end of the treatment period (all animals)

Electrolytes

Calcium	✓ Potassium
✓ Chloride	✓ Sodium
Phosphorus (inorganic)	

Metabolites and Proteins

Albumin	Globulin
A/G ratio	✓ Glucose
✓ Bilirubin (total)	✓ Protein (total)
Cholesterol	✓ Urea
Creatinine	✓ Protein electrophoresis

Enzymes:

	✓ Lactate dehydrogenase (LDH)
✓ Alanine aminotransferase (ALT)	✓ Alkaline phosphatase (ALP)
✓ Aspartate aminotransferase (AST)	✓ γ-glutamyl transpeptidase (γ-GT)

Urinalysis: nor performed

Pathology: The following organs were collected (column C), weighed (W) and examined histopathologically (H) from all individuals.

C	W	H		C	W	H	
✓	✓	✓	adrenals	✓	✓	✓	pituitary
			aorta	✓		✓	prostate
✓	✓	✓	brain				rectum
✓		✓	caecum	✓		✓	salivary gland
✓		✓	colon				
✓		✓	duodenum				seminal vesicles
			epididymides	✓		✓	skin (treated and untreated)
✓		✓	esophagus	✓		✓	spinal cord
✓		✓	eyes	✓		✓	spleen

		femur (with joint)	✓	✓	sternum with bone marrow
✓	✓	gross lesions	✓	✓	stomach
✓	✓	✓ heart	✓	✓	✓ testis
✓		✓ ileum	✓	✓	thymus
✓		✓ jejunum	✓	✓	✓ thyroid/parathyroid
✓	✓	✓ kidneys	✓	✓	trachea
		lacrymal glands	✓	✓	urinary bladder
✓	✓	✓ liver	✓	✓	uterus
✓		✓ lung			
✓		✓ lymph nodes			*others:*
		mammary gland (female)			muzzle
✓		✓ muscle, skeletal			orbital gland
✓		✓ nerve, peripheral			tongue
✓	✓	✓ ovary			Zymbal gland
✓		✓ pancreas			body (exsanguinated)

13 Findings

Mortality: No mortality occurred.

Clinical signs: At 1'000 mg/kg and above, dyspnea, tremor, ataxia, sedation and ruffled fur were noted from days 4 onwards.

xLocal irritation: In all treated groups, slight irritation was noted at the application site.

xBody weight: A minimally reduced body weight gain was noted in the top dose group animals.

Food consumption: No changes.

xHematology: An increased plasma bilirubin concentration was noted in the top dose group males. In the absence of any effect in the females, no toxicological significance was attributed to the finding.

xClinical chemistry: No changes.

xOrgan weights: Increased absolute and relative liver weights were noted in both sexes treated at 5'000 mg/kg.

Pathology: The application site showed chronic inflammatory changes, focal acanthosis and hyperkeratosis with a dose-related increasing incidence and severity. Some individuals from the top dose group had necroses and ulcerations, in addition. The intensity of the dermal changes in the low dose group animals was similar to that seen in several control rabbits. The slight changes in this groups were therefore attributed to the occlusive administration procedure. No other treatment related changes were noted.

NOEL: The NOEL for systemic toxicity was 200 mg/kg. Slight skin irritation was still observed at this low dose level.

14 Statistics Uni-variate analysis. Comparison to controls by Lepage-test, trend analysis by the Jonckheere t-test.

15 (published) References none

16 data Unpublished none

x17 Indicator Reliability 1

Data Protection Claim	Yes

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	19.1.2005
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	[redacted]

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

98/8 Doc IIIA section No.	**6.3.2/02**	**Repeated dose toxicity (dermal)**
91/414 Annex Point addressed	**II 5.3.3 / 01**	Short-term btoxicity - other routes
1.2	**Title**	CGA 64'250 techn.: 28 day Repeated Dose Dermal Toxicity Study in Rats
1.3	**Report and/or project N° Syngenta File N° (SAM)**	993102 64250 / 4412
1.4	**Lab. Report N°**	-
1.5	**91/414 Cross Reference to original study / report**	5.3.3 / 01
1.6	**Authors**	Report: [redacted]
1.7	**Date of report**	March 20, 2001
1.8	**Published / owner**	Unpublished / Syngenta
2.1	**Testing facility**	[redacted]
x2.2	**Dates of experimental work**	September 30 to October 19, 1999
3.	**Objectives**	Investigation of cumulative dermal toxicity in rats
4.1	**Test substance**	CGA 64'250, technical grade active ingredient
x4.2	**Specification**	[redacted]
4.3	**Storage stability**	stable at room temperature
4.4	**Stability in vehicle**	stable
4.5	**Homogeneity in vehicle**	homogene
4.6	**Validity**	not applicable
x5	**Vehicle / solven**	Distilled water, 1% CMC, 0.1 Tween 80
6	**Physical form**	viscous liquid
7.1	**Test method**	OECD 410
7.2	**Justification**	Not applicable
7.3	**Copy of method**	On request
8	**Choice of method**	not applicable
9	**Deviations from EC-Directive 92/69 B9**	Not applicable
10.1	**Certified laboratory**	not applicable
10.2	**Certifying authority**	not applicable
10.3	**GLP**	yes
10.4	**Justification**	Not applicable
11.1	**GEP**	not applicable

11.2 Type of facility (official or officially recognised) [redacted]

11.3 Justification not applicable

x12 Test system

Animal species: Albino Rat (Hanl bm:WIST (SPF))
Source: [redacted]
Dose levels: 0, 10, 100, 1000 mg/kg
Group size: 40 males and 40 females
Age/weight: 141 – 228 gr
Administration: Dermal application to shaved skin under occlusive dressing for 6 hours to an area of at least 10% of the body surface
Study duration: 6 weeks
General study
Design: Daily treatment, 5 days per week for 3 weeks, and 7 days the 4th week
Mortality: Twice daily
Clinical signs: Daily
Local irritation: 17 hours after completion of each treatment
Body weight: day 1,8,15,22,28
Food consumption: Weekly
Hematology: At the end of the treatment period (all animals)

Red blood cells
- ✓ Erythrocyte count (RBC)
- ✓ Hemoglobin (Hb)
- ✓ Hematocrit (Hct)
- ✓ Mean corp. volume (MCV)
- ✓ Mean corp. hemoglobin (MCH)
- ✓ Heinz Bodies
- ✓ Reticulocytes
- ✓ Methemoglobin

White blood cells
- ✓ Total leukocyte count
- ✓ Neutrophils (differential)
- ✓ Eosinophils (differential)
- ✓ Basophils (differential)
- ✓ Lymphocytes (differential)
- ✓ Monocytes (differential)
- Large unstained cells (diff.)

Clotting Potential
- ✓ Prothrombine time
- ✓ Partial thromboplastin time
- ✓ Thrombocyte count

Urinalysis: nor performed

Pathology: The following organs were collected (column C), weighed (W) and examined histopathologically (H) from all individuals.

C	W	H		C	W	H	
✓	✓	✓	Adrenals	✓	✓	✓	pituitary
✓		✓	Aorta	✓		✓	prostate
✓	✓	✓	Brain				rectum
✓		✓	Caecum	✓		✓	salivary gland
✓		✓	Colon				
✓		✓	Duodenum				seminal vesicles
✓		✓	Epididymides	✓		✓	Skin (treated and untreated)
✓		✓	Esophagus	✓		✓	spinal cord
✓		✓	Eyes	✓	✓	✓	spleen
✓		✓	femur (with joint)	✓		✓	sternum with bone marrow
			gross lesions	✓		✓	stomach
✓	✓	✓	Heart	✓	✓	✓	testis
			Ileum	✓	✓	✓	thymus
			Jejunum	✓	✓	✓	thyroid/parathyroid
✓	✓	✓	Kidneys	✓		✓	trachea
✓		✓	lacrymal glands	✓		✓	urinary bladder
✓	✓	✓	Liver	✓	✓	✓	uterus
✓		✓	Lung				
✓		✓	lymph nodes				*others:*
✓		✓	mammary gland (female)				muzzle
✓		✓	muscle, skeletal				orbital gland
✓		✓	nerve, peripheral				tongue
✓	✓	✓	ovary				
✓		✓	pancreas				

x13 Findings

Mortality: No mortality occurred.

Clinical signs: No clinical signs were observed.

xLocal irritation: No occurrence of local irritation was observed.

Table 6.3.2/02 Microscopic findings at the application site: incidence and grading. (added by RMS)

		Males				**Females**			
Skin at the applica-tion site	Dose mg/kg	**0**	**10**	**100**	**1000**	**0**	**10**	**100**	**1000**
	No. Exam.	10	10	10	10	10	10	10	10
Acanthosis									
grade 1		8	7	9	8	1	3	0	8
grade 2		1	0	0	2	0	0	0	0
Hydropic change									
grade 1		1	2	1	0	0	0	0	0
Hyperkeratosis									
Grade 1		1	4	8	6	2	0	1	1

This table is a modification of a tble presented in the test report. Grade 1=minimal ; grade 2=slight

Body weight: No changes.

Food consumption: No changes.

Hematology: Treatment had no effect on the hematological profile of the rats.

xBlood chemistry Slightly higher values for protein and globulin with an associated decrease in the albumin to globulin ratio were recorded for females at 1000 mg/kg. In addition, females of group 4 (1000 mg/kg) had an increased cholesterol level and females of group 3 and 4 (100 and 1000 mg/kg) had lower values for chloride. The blood chemistry profile of treated males was not disturbed by treatment.

Clinical chemistry: No changes.

xOrgan weights: The mean absolute/relative liver weights were increased in high dose males (+19%/+15%) and females (+14%/+10%).

No other treatment-related effects were noted.

xPathology: Dermal treatment with the test item over a period of 4 weeks was well tolerated by the rats at all tested dose levels. There were no signs of overt toxicity. At dose levels of 1000 and 100 mg/kg, few blood chemistry parameters were changed in females only, and in both sexes the mean liver weights were increased at 1000 mg/kg. These findings point to the occurrence of adaptive metabolic processes. At the site of application increased incidence of minimal acanthosis was detected in females (1000 mg/kg). Due to the obvious adaptive nature of all observed effects, they were considered to be not adverse.

NOEL: The NOEL was at 10 mg/kg body weight and the NOAEL was defined at 1000 mg/kg body weight.

14	**Statistics**	Parametric and non-parametric statistical tests. Comparison to controls by Dunnett's multiple comparison test.
15 (published)	**References**	None
16 data	**Unpublished**	None
17 Indicator	**Reliability**	1

Data Protection Claim	Yes

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	21.1.2005
Materials and Methods	[redacted]

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

Remarks	[redacted]

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

98/8 Doc IIIA section No.	6.3.3	Repeated dose toxicity (inhalation)

[redacted]

	Evaluation by Competent Authorities
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	4.2.2005
Conclusion	[redacted]
Acceptability	[redacted]
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

98/8 Doc IIIA section No.	**6.4.1/01**	**Subchronic oral toxicity test**
91/414 Annex Point addressed	**II 5.3.2 / 01**	Short-term toxicity - oral 90-day studies

1.2	**Title**	CGA 64'250 techn.: Three months toxicity study on rats
1.3	**Report and/or project N° Syngenta File N° (SAM)**	79 00 14 64250 / 1538
1.4	**Lab. Report N°**	79 00 14
1.5	**91/414 Cross Reference to original study / report**	5.3.2 / 01
1.6	**Authors**	Report: [redacted] Summary:
1.7	**Date of report**	August 30, 1979
1.8	**Published / owner**	Unpublished / Syngenta
2.1	**Testing facility**	[redacted]
2.2	**Dates of experimental work**	January 15 to April 17, 1979
3.	**Objectives**	Investigation of short-term toxicity in rats
4.1	**Test substance**	CGA 64'250, technical grade active ingredient
x4.2	**Specification**	[redacted]
4.3	**Storage stability**	The a.i. is known to be stable at room temperature.
4.4	**Stability in vehicle**	Confirmed. Prior to the initiation of the study and after the end of the treatment period diet samples were analysed. Mean concentrations in all samples were in the range of 87 to 95% of the intended values.
4.5	**Homogeneity in vehicle**	Not specifically tested. As all samples analysed were in the same concentration range, a homogeneous mixture was achieved.
4.6	**Validity**	not applicable
5	**Vehicle / solven**	The test substance was admixed to the powdered standard diet. 12% of water was added and the mixture was pelleted. Pellets were air dried.
6	**Physical form**	viscous liquid
7.1	**Test method**	not specified
7.2	**Justification**	The study was conducted before the OECD Guideline 408 was released
7.3	**Copy of method**	Methodological details are part of the original report submitted under 5.3.2 / 01
8	**Choice of method**	not applicable
9	**Deviations from EC-Directive 87 / 302 B**	Not all of the suggested biochemical parameters were investigated. Formal deviations are outlined below.
10.1	**Certified laboratory**	not applicable
10.2	**Certifying authority**	not applicable
10.3	**GLP**	No

10.4	**Justification**	The study was performed before GLP regusltions were enacted.
11.1	**GEP**	not applicable
11.2	**Type of facility (official or officially recognised)**	[redacted]
11.3	**Justification**	not applicable

x12 Test system

Animal species: Rat, Tif RAIf (SPF)
Source: [redacted]
Dose levels: 0, 240, 1'200 and 6'000 ppm (= mg/kg diet)
Group size: 20 males and 20 females
Age/weight: Young adult (4 weeks), 123-125 g (males) and 111-116g (females)
Administration: Oral with the diet
Study duration: 28 days
General study
Design: Continuous dietary treatment over 3 months
Mortality: Twice daily
Clinical signs: Daily
Ophthalmology: Pretest and before sacrifice in all individuals
Hearing test: Pretest and before sacrifice in all individuals
Body weight: Weekly
Food consumption: Weekly
Hematology: After 4, 8 and 13 weeks (10 animals per sex and group)

Red blood cells

✓ Erythrocyte count (RBC)	✓ Mean corp. hemoglobin (MCH)
✓ Hemoglobin (Hb)	Mean corp. Hb. conc. (MCHC)
✓ Hematocrit (Hct)	Red cell vol. distr. width (RDW)
✓ Mean corp. volume (MCV)	Hb conc. distr. width (HDW)

White blood cells

✓ Total leukocyte count	✓ Lymphocytes (differential)
✓ Neutrophils (differential)	✓ Monocytes (differential)
✓ Eosinophils (differential)	Large unstained cells (diff.)
✓ Basophils (differential)	

Clotting Potential

✓ Prothrombine time	✓ Thrombocyte count

Clinical chemistry: After 4, 8 and 13 weeks (10 animals per sex and group)

Electrolytes

Calcium	✓ Potassium
✓ Chloride	✓ Sodium
Phosphorus (inorganic)	

Metabolites and Proteins

Albumin	Globulin
A/G ratio	✓ Glucose
Bilirubin (total)	✓ Protein (total)
Cholesterol	✓ Urea
Creatinine	✓ Protein electrophoresis

Enzymes:

	✓ Lactate dehydrogenase (LDH)
✓ Alanine aminotransferase (ALT)	✓ Alkaline phosphatase (ALP)
✓ Aspartate aminotransferase (AST)	✓ γ-glutamyl transpeptidase (γ-GT)

Urinalysis: After 4, 8 and 13 weeks (10 animals per sex and group)

Quantitative parameters:

✓ Urine volume	✓ pH-value
✓ Relative density	

Semiquantitative parameters:

✓ Bilirubin	✓ Ketones
✓ Blood	✓ Protein
✓ Color	✓ Urobilirubin
✓ Glucose	✓ Sediment

Pathology: The following organs were collected (column C), weighed (W) and examined histopathologically (H) from all individuals.

C	W	H		C	W	H	
✓	✓	✓	adrenals				pituitary
			aorta	✓		✓	prostate

✓	✓	✓	brain				rectum
			caecum	✓		✓	salivary gland
✓		✓	colon				
✓		✓	duodenum				seminal vesicles
			epididymides	✓		✓	skin
✓		✓	esophagus	✓		✓	spinal cord
✓		✓	eyes	✓		✓	spleen
			femur (with joint)	✓		✓	sternum with bone marrow
			gross lesions	✓		✓	stomach
✓	✓	✓	heart	✓	✓	✓	testis
✓		✓	ileum	✓		✓	thymus
✓		✓	jejunum	✓		✓	thyroid/parathyroid
✓	✓	✓	kidneys	✓		✓	trachea
			lacrymal glands	✓		✓	urinary bladder
✓	✓	✓	liver	✓		✓	uterus
✓		✓	lung				
✓		✓	lymph nodes				*others:*
			mammary gland (female)				muzzle
✓		✓	muscle, skeletal				orbital gland
✓		✓	nerve, peripheral				tongue
✓	✓	✓	ovary				Zymbal gland
✓		✓	pancreas				body (exsanguinated)

x13 Findings

Mortality: No mortality occurred.

Clinical signs: No symptoms were noted during the study.

Ophthalmology: No treatment-related changes.

Hearing test: No treatment-related changes.

xBody weight: A significantly reduced body weight gain was noted in both sexes from the top dose group and in the females treated at 1'200 ppm CGA 64'250.

xFood consumption: No treatment-related changes.

xHematology: Red blood cell parameters (RBC, Hb, Hct) were slightly but consistently reduced in both sexes treated at 6'000 ppm.

xClinical chemistry: In the top dose group, the serum activity of the γ-GT was increased in males and females. The females showed a higher ALP activity at week 13.

Urinalysis: No treatment-related changes.

Organ weights: No treatment-related changes. Differences in organ weights were considered to be secondary to the reduced body weight in intermediate dose group females and top dose groups.

xPathology: A slight hemosiderosis of the spleen was noted in females receiving 6'000 mg/kg CGA 64'250

NOEL: The NOEL was 240 ppm, estimated to be equivalent to a mean daily intake of 15.9 mg/kg propiconazole in males and 16.8 mg/kg in females, respectively.

14	**Statistics**	Uni-variate analysis. Comparison to controls by Lepage-test, trend analysis by the Jonckheere t-test.
15 (published)	**References**	none
16 data	**Unpublished**	none
x17 Indicator	**Reliability**	1

Data Protection Claim	Yes

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	20.1.2005
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	[redacted]

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

PP 2.504 / WM / 25.10.1994

98/8 Doc IIIA section No.	**6.4.1/02**	**Subchronic oral toxicity test**
91/414 Annex Point addressed	**II 5.3.2 / 02**	Short-term toxicity - oral 90-day studies

1.2	**Title**	CGA 64'250 techn.: 3-month toxicity study on dogs
1.3 project N° Syngenta File N° (SAM)	**Report and/or**	78 57 51 64250 / 1539
x1.4	**Lab. Report N°**	78 58 51
1.5 Reference to original study / report	**91/414 Cross**	5.3.2 / 02
1.6	**Authors**	Report: [redacted] Summary:
1.7	**Date of report**	August 9, 1979
1.8 owner	**Published /**	Unpublished / Syngenta
2.1	**Testing facility**	[redacted]
2.2 experimental work	**Dates of**	December 18, 1978 to March 19, 1979
3.	**Objectives**	Investigation of short-term toxicity in dogs
4.1	**Test substance**	CGA 64'250, technical grade active ingredient
x4.2	**Specification**	[redacted]
4.3	**Storage stability**	The a.i. is known to be stable at room temperature.
4.4 vehicle	**Stability in**	Confirmed. Diet samples were analysed in week 1, 5, 8 and 13. Mean concentrations in all groups were in the range of 92 to 97% of the nominal values.
4.5 vehicle	**Homogeneity in**	Not specifically tested. As all samples analysed were in the same concentration range, a homogeneous mixture was achieved.
4.6	**Validity**	not applicable
5	**Vehicle / solven**	The test substance was admixed to the powdered standard diet. 18 % of water was added and the mixture was pelleted. Pellets were air dried.
6	**Physical form**	viscous liquid
7.1	**Test method**	not specified
7.2	**Justification**	The study was conducted before the OECD Guideline 409 was released
7.3	**Copy of method**	Methodological details are part of the original report submitted under 5.3.2 / 02
8 method	**Choice of**	not applicable
9 EC-Directive 87 / 302 B	**Deviations from**	Not all of the suggested biochemical parameters were investigated. Formal deviations are outlined below.
10.1 laboratory	**Certified**	not applicable
10.2 authority	**Certifying**	not applicable
10.3	**GLP**	no
10.4	**Justification**	not applicable