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: Dog, pedigree Beagle
Source: [redacted]
Dose levels: 0, 50, 250 and 1'250 ppm (= mg/kg diet)
Group size: 4 males and 4 females
Age/weight: 19-28 weeks, 7.9-13kg (males) and 6.0-11.6kg (females)
Administration: Oral uptake through the diet.
Study duration: 92 days
General study
Design: Dietrary administration of the test substance
Mortality: Daily
Clinical signs: Daily
Ophthalmology: Pretest and before sacrifice in all individuals
Hearing test: Weekly
Body weight: Weekly
Food consumption: Weekly
Hematology: Pretest and at weeks 4, 8 and 13.

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: Pretest and at weeks 4, 8 and 13.

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

Urinalysis: Pretest and at weeks 4, 8 and 13.

Quantitative parameters:

Urine volume	✓ pH-value
✓ Relative density	

Semiquantitative parameters:

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

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

x13 Findings

Mortality: No mortality occurred.

Clinical signs: No treatment-related clinical symptoms were noted.

Ophthalmology: No treatment-related changes.

Hearing test: No treatment-related changes.

Body weight: No treatment-related changes.

xFood consumption: No treatment-related changes.

xHematology: No treatment-related changes.

xClinical chemistry: No treatment-related changes.

Urinalysis: No treatment-related changes.

xOrgan weights: No treatment-related changes.

xPathology: At necropsy, three males from the top dose group showed a granular surface of the pyloric and pre-pyloric region of the stomach. The changes were histopathologically identified as slightly increased amounts of lymphoid follicles in the mucous membrane.
One female from the 250 ppm dose group was similarly affected.
These changes were considered to be of spontaneous origin.

xNOEL: In the original report, the NOEL was considered to be 1'250 ppm. However, with regard to the changes observed in the stomach of the males from the top dose group, a conservative NOEL of 250 ppm is proposed, corresponding to a mean daily intake of 6.9 mg/kg propiconazole.

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	24.1.2005
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	[redacted]

Table 6.4 [redacted]

[redacted]	[redacted]			
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				

[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.	6.4.1/03	Subchronic oral toxicity test
91/414 Annex Point addressed	II 5.3.2 / 03	Short-term toxicity - oral 90-day studies

1.2	Title	Subchronic dietary toxicity study with CGA 64'250 in mice
1.3	Report and/or project N° Syngenta File N° (SAM)	F-00098 64250 / 2020
1.4	Lab. Report N°	F-00098
1.5	91/414 Cross Reference to original study / report	5.3.2 / 03
1.6	Authors	Report: [redacted] Summary:
1.7	Date of report	April 30, 1991
1.8	Published / owner	Unpublished / Syngenta
2.1	Testing facility	[redacted]
x2.2	Dates of experimental work	March 3 to July 13, 1990
3.	Objectives	Investigation of liver effects in mice
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. The mixture was stable at room temperature as well as at 4°C for at least 40 days.
4.5	Homogeneity in vehicle	Confirmed. Samples from all diet blends were analysed for the content. Six samples from each dose level (two from bottom, left and right of the batch) and one control sample were analysed for homogeneity.
4.6	Validity	not applicable
5	Vehicle / solven	The test substance was admixed to the powdered standard diet.
6	Physical form	viscous liquid
7.1	Test method	According to the U.S. FIFRA Subdivision F, §82-1
7.2	Justification	standard method
7.3	Copy of method	standard protocol
8	Choice of method	standard method
9	Deviations from EC-Directive 87 / 302 B	As it was the main purpose of the study, to investigate effects on the liver morphology, no hematological investigations were conducted and blood biochemistry was confined to relevant parameters. Histopathology was confined to the liver.
10.1	Certified laboratory	yes
10.2	Certifying authority	U.S. Environmental Protection Agency
10.3	GLP	yes

10.4	**Justification**	not applicable
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: Mouse, Crl:CD-1
Source: [redacted]
Dose levels: 0, 20, 500, 850, 1'450 and 2'500 ppm (males)
0, 20, 500, 2'500 ppm (females)
Group size: 20 males and 20 females
Age/weight: Young adult (7 weeks), 24.6-39.0 g (males) and 19.7-27.0 g (females)
Administration: Oral with the diet
Study duration: 17 weeks
General study
Design: Continuous dietary treatment over 4 months
Mortality: Twice daily
Clinical signs: Twice daily
Ophthalmology: not conducted
Hearing test: not conducted
Body weight: Weekly
Food consumption: Weekly
Hematology: not conducted

Clinical chemistry: After 13 and 17 weeks (20 animals per sex and group)

Metabolites and Proteins

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

Enzymes:

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

Urinalysis: not conducted

x

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	✓			pancreas
✓			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)	✓			gall bladder
✓			ovary				Zymbal gland
✓			pancreas				body (exsanguinated)

x13 **Findings**

xMortality: Two males (one from the 20 ppm and the other from the 850 ppm dose group) were terminated due to poor general conditon. The cases were not related to the treatment.

Clinical signs: No symptoms were noted during the study.

xOphthalmology: Not investigated

Hearing test: Not investigated

xBody weight: A significanty reduced body weight and body weight gain was noted in the top dose group males after 12 and 17 weeks.

Food consumption: No treatment-related changes.

Hematology: Not investigated

xClinical chemistry: Reduced serum concentrations of cholesterol were noted in the males treated at 850 ppm and above. Increased ALAT activities were found in males treated at 1'450 ppm and above and in the females treated at 2'500 ppm. In the top dose group females, the ASAT activities were also increased.

Urinalysis: Not investigated.

xOrgan weights: Increased absolute and relative liver weights were noted in males treated at 500 ppm and above and in the top dose group females.

xPathology: Hepatocellular hypertrophy was observed in the males treated at 850 ppm and above and in females receiving 2'500 ppm propiconazole. Hepatocellular necroses occurred in the males at 1'450 ppm and above and in the top dose group females. Hepatocellular vacuolation was noted in the top dose group males.

NOEL: The NOEL was 20 ppm in males and 500 ppm in females.

14	**Statistics**	One-way analysis of variance on food consumption, body weight, clinical chemistry and organ weight data (ANOVA). Dunnett t-test was applied, in addition. A trend statistics (Terpstra-Jonckheere) was applied to body weight gain data from the males. Incidence data from histopathology were analysed by the Fischer exact probability 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	25.1.2005
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]

TABLE 6.4.1/03-1

[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]

	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.	**6.4.1/04**	**Subchronic oral toxicity test**
91/414 Annex Point addressed	**II 5.3.2 / 04**	Short-term toxicity - oral 90-day studies

1.2	**Title**	13-week dietary toxicity study with CGA 64'250 in male mice
1.3	**Report and/or project N° Syngenta File N° (SAM)**	F-00107 64250 / 2019
1.4	**Lab. Report N°**	F-00107
1.5	**91/414 Cross Reference to original study / report**	5.3.2 / 04
1.6	**Authors**	Report: [redacted] Summary:
1.7	**Date of report**	April 30, 1991
1.8	**Published / owner**	Unpublished / Syngenta
2.1	**Testing facility**	[redacted]
2.2	**Dates of experimental work**	July 18 to October 19, 1990
3.	**Objectives**	Investigation of liver effects in male mice
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. The mixture was stable at room temperature as well as at 4°C for at least 40 days.
4.5	**Homogeneity in vehicle**	Confirmed. Samples were analysed for content and homogeneity after the first blend and monthly thereafter.
4.6	**Validity**	not applicable
5	**Vehicle / solven**	The test substance was admixed to the powdered standard diet.
6	**Physical form**	viscous liquid
7.1	**Test method**	According to the U.S. FIFRA Subdivision F, §82-1
7.2	**Justification**	standard method
7.3	**Copy of method**	standard protocol
8	**Choice of method**	standard method
9	**Deviations from EC-Directive 87 / 302 B**	It was the main purpose of the study, to investigate the onset of effects on the liver morphology and liver function. Therefore, no hematological investigations were conducted and blood biochemistry was confined to relevant parameters. Histopathology was confined to the liver.
10.1	**Certified laboratory**	yes
10.2	**Certifying authority**	U.S. Environmental Protection Agency
10.3	**GLP**	yes

10.4	**Justification**	not applicable
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: Mouse, Crl:CD-1
Source: [redacted]
Dose levels: 0, 20, 500, 850, 1'450 and 2'500 ppm
Group size: 40 males
Age/weight: Young adult (5 weeks), 21.4-31.2 g
Administration: Oral with the diet
Study duration: 13 weeks
General study
Design: Continuous dietary treatment over 13 weeks. Interim sacrifices of 10 animals per dose group after 4 and 8 weeks of treatment.
Mortality: Twice daily
Clinical signs: Twice daily
Ophthalmology: not conducted
Hearing test: not conducted
Body weight: Weekly
Food consumption: Weekly
Hematology: not conducted

Clinical chemistry: After 4 and 8 weeks (n=10) and at termination aftre 13 weeks

Metabolites and Proteins
✓ Cholesterol
Enzymes:
✓ Alanine aminotransferase (ALT) ✓ Alkaline phosphatase (ALP)
✓ Aspartate aminotransferase (AST) ✓ Sorbitol dehydrogenase (SDH)

Urinalysis: not conducted

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

C	W	H		C	W	H	
✓	✓	✓	liver	✓	✓		brain

x13 Findings

Mortality, clinical signs: No mortality or clinical signs occurred.

Body weight: Reduced body weight and weight gain in the top dose group.

Food consumption: No treatment-related changes.

Clinical chemistry: Serum cholesterol concentrations reduced at 500 ppm and above. ALAT activity increased at 1'450 ppm and above. SDH activity increased at 850 ppm and above. The changes were observed already after 4 weeks.

Organ weights: Increased absolute and relative liver weights at 500 ppm and above. The changes were observed at all sacrifices.

xPathology: Increased incidences of hepatocellular hypertrophy at 500 ppm and above. Necroses were observed from 850 ppm onwards, vacuolation at 1'450 ppm and higher and mineralization in the top dose group only.

NOEL: The NOEL was 20 ppm, equivalent to a mean daily intake of 2.8 mg/kg propiconazole.

14	**Statistics**	ANOVA, Dunnett t-test, Terpstra-Jonckheere t-test, Fischer exact probability 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	8.2.2005
Materials and Methods	Point 12: For comparison to other studies, the mouse strain used in this study was Crl:CD-1 (ICR)BR(Swiss). Dose levels: The dose levels expressed in ppm were equivalent to 2.8, 71, 121, 199 and 360 mg/kg bw/day.
Results and discussion	Point 13: The reported changes in body weight, clinical chemistry, organ weights and incidences of histopathological findings are statistically significant, with the exception that statistically significant increase in necrotic lesions was observed only from ≥ 1450 ppm dose. Necrosis at doses of 500 and 850 ppm may, however, also show a biologically relevant increase. Gross necropsy of livers revealed statistically significant enlargement (≥ 850 ppm), focal discoloration (≥ 850 ppm) and prominent lobular architecture (≥ 1450 ppm). Gross pathology and histological findings are presented in Tables 6.4.1/04-1 and 6.4.1/04-2, added by the RMS.
Conclusion	The findings of this study were very similar to the previous subchronic mouse study (6.4.1/03). The effects on the liver were seen at the same dose level in both studies. Furthermore, this study revealed that increased liver weights and changes in clinical chemistry parameters relevant to liver were already seen after 4 weeks of exposure. The MTD was lower in this study. RMS agrees with the applicant on the NOAEL-values. Based on hepatocellular hypertophy and increased liver weights the NOAEL-value was 2.8 mg/kg bw/day (20 ppm). The MTD was 850 ppm.
Reliability	2
Acceptability	Acceptable as a subchronic liver toxicity study in male mice.
Remarks	Due to the rather specific aim of the study only selected parameters were measured and examinations performed, but the protocol is otherwise comparable with OECD Guideline 408 and directive 67/548 (Annex V) method B.26 requirements. The study is done under GLP. Due to the narrow scope of the study RMS disagrees with applicant in assessment of reliability. The reliability indicator in IUCLID is to be changed from 1 to 2. It is noteworthy that the [redacted] This study is missing from IUCLID.

TABLE 6.4.1/04-1

[redacted]

[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						

[redacted]

	[redacted]					
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						

[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 / 26.10.1994

98/8 Doc IIIA section No.	6.4.2	Subchronic dermal toxicity test

A justification for the absence of a 90-day dermal study is required and is provided below.

[redacted]

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	16.8.2005
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.	**6.4.3**	**Subchronic inhalation toxicity test**
91/414 Annex Point addressed	**II 5.3.3 / 02**	Short-term toxicity - other routes

1.2	**Title**	CGA 64'250 techn.: 90 days aerosol inhalation toxicity study in rats
1.3	**Report and/or project N° Syngenta File N° (SAM)**	79 00 06 64250 / 1593
1.4	**Lab. Report N°**	79 00 06
1.5	**91/414 Cross Reference to original study / report**	5.3.3 / 02
1.6	**Authors**	Report: [redacted] Summary:
1.7	**Date of report**	Sepember 10, 1980
1.8	**Published / owner**	Unpublished / Syngenta
2.1	**Testing facility**	[redacted]
x2.2	**Dates of experimental work**	August 27 to December 3, 1979
3.	**Objectives**	Investigation of subchronic inhalation 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**	Propiconazole is stable in acetone.
4.5	**Homogeneity in vehicle**	Propiconazole is soluble in acetone.
4.6	**Validity**	not applicable
5	**Vehicle / solven**	acetone
6	**Physical form**	viscous liquid
7.1	**Test method**	K. Sachsse, L. Ullmann, G. Voss, R. Hess: Measurement of inhalation toxicity of aerosols in small laboratory animals. In: Proceedings of the Europ. Soc. for the Study of Drug Toxicity. Vol. XV, 239-251, Zürich, June 1973. K. Sachsse, L. Ullmann, K. Zbinden: Toxikologische Prüfungen von Aerosolen im Tierexperiment. Chemische Rundschau 29 (38), p 1ff, 1976.
7.2	**Justification**	The study was conducted before the OECD Guideline 413 was released. The protocol used is in accordance with sound scientific principles.
7.3	**Copy of method**	Methodological details are part of the original report submitted under 5.3.3 / 02. Further details are given in the above references.
8	**Choice of method**	The method is in accordance with sound scientific principles.
9	**Deviations from EC-Directive 87/302 B**	The number of animals used ist higher than requested. Not all suggested parameters of blood biochemistry were investigated. Further, 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	**Type of facility (official or officially recognised)**	[redacted]
11.3	**Justification**	not applicable

x12 **Test system**

Animal species: Rat, Tif RAIf (SPF)
Source: [redacted]
xDose levels: 0 (negative control), 10 mg/m^3 acetone (vehicle control), 20, 80 and 200 mg/m^3 propiconazole (nominal concentration)
Group size: 20 males and 20 females
Age/weight: Young adult (7 weeks), 216-227 g (males) and 184-192g (females)
Administration: Inhalation (nose only) for 6 hours per day, 5 days per week.
Study duration: 90 days
General study
Design: Daily treatment 5 days per week for 13 weeks.
Aerosol quality: Daily determination of temperature, humidity, flow rate, oxigen, particle size distribution and concentration of test article.
Mortality: Twice daily
Clinical signs: Daily
xOphthalmology: Pretest and before sacrifice in all individuals
Body weight: Weekly
Food consumption: Weekly
Hematology: At week 6 and at termination (10 animals per sex and group)

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

xClinical chemistry: At week 6 and at termination (10 animals per sex and group)

Electrolytes
- Calcium
- ✓ Chloride
- Phosphorus (inorganic)
- ✓ Potassium
- ✓ Sodium

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

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

Urinalysis: not conducted

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)	✓		✓	nasal passages
✓		✓	muscle, skeletal	✓		✓	paranasal recesses
✓		✓	nerve, peripheral				tongue
✓		✓	ovary				Zymbal gland
✓		✓	pancreas				body (exsanguinated)

x13 Findings

Inhalation atmosphere

Exposure Group	**air**	**acetone**	**20**	**80**	**200**
Actual conc. in breathing zone (mg/m^3)	-	10	21 ± 2	85 ± 7	191 ± 10
Mass Median Aerodyn. Diameter	-	over 80% of particles smaller than 7 Om			
Air flow (m/sec)	0.4	0.41	0.4	0.4	0.41
Chamber Temperature	24.8 °C	24.9 °C	24.8 °C	24.9 °C	24.9 °C
Oxygen content	20.3%	20.4%	20.4%	20.3%	20.2%
Relative humidity	63.9%	66.3%	66.3%	65.9%	64.5%

Mortality: Two males from negative controls and one female from the low dose group died spontaneously. The cases were not related to the treatment.

Clinical signs: No symptoms were noted during the study.

Ophthalmology: No treatment-related changes.

xBody weight: A slightly reduced body weight gain was noted in the females from the top dose and low dose groups exposed to 21 and 190 mg/m^3. Similar deviations were noted in the intermediate dose group males.

Food consumption: No teatment-related changes.

Hematology: No teatment-related changes.

xClinical chemistry: No teatment-related changes.

xOrgan weights: No teatment-related changes.

xPathology: No teatment-related changes.

xNOEL: Considered formally, no NOEL was defined for the females. However, in the absence of a dose-effect relationship, the toxicological significance of the body weight effects is questionable.

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

15 References (published) none

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

Data Protection Claim	Yes

Evaluation by Competent Authorities

EVALUATION BY RAPPORTEUR MEMBER STATE

Date 24.2.2005

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 / 26.10.1994

98/8 Doc IIIA section No.	**6.6.1**	**In-vitro gene mutation study in bacteria**
91/414 Annex Point addressed	**II 5.4.1 / 01**	Genotoxicity Studies - *In vitro* testing

1.2	**Title**	Salmonella / mammalian microsome mutagenicity test
1.3	**Report and/or project N° Syngenta File N° (SAM)**	830121 64250 / 1571
1.4	**Lab. Report N°**	830121
1.5	**91/414 Cross Reference to original study / report**	5.4.1 / 01
1.6	**Authors**	Report: [redacted] Summary:
1.7	**Date of report**	June 27, 1983
1.8	**Published / owner**	unpublished / Syngenta Ltd. Basle / Switzerland
2.1	**Testing facility**	[redacted]
2.2	**Dates of experimental work**	March 1, 1983 to March 24, 1983
3.	**Objectives**	Detection of point mutations in bacteria with and without metabolic activation of the test substance.
4.1	**Test substance**	CGA 64'250, technical grade active ingredient
4.2	**Specification**	[redacted]
4.3	**Storage stability**	The a.i. is known to be stable at room temperature.
4.4	**Stability in vehicle**	not investigated. The solutions were freshly prepared before use.
4.5	**Homogeneity in vehicle**	not applicable
4.6	**Validity**	not applicable
5	**Vehicle / solven**	DMSO
6	**Physical form**	viscous liquid
7.1	**Test method**	The test was carried out according to the method desribed by Ames et al. (see below)
7.2	**Justification**	The study was conducted before the OECD Guideline 471 was released.
7.3	**Copy of method**	Methodological details are part of the original report submitted under 5.4.1 / 01
8	**Choice of method**	The method used is in compliance with sound scientific principles.
9	**Deviations from EC-Directive 92/69, B.14**	Testing of strain TA 1538 is not required. Positive control substances used without metabolic activation were: For TA 1535: N-methyl-N'-nitro-N-nitrosoguanidine For TA 98: Daunoblastine For TA 100: 4-nitroquinoline-N-oxide. With metabolic activation: For TA 100: Cyclophosphamide
10.1	**Certified laboratory**	no

10.2	**Certifying authority**	not applicable
10.3	**GLP**	yes
10.4	**Justification**	Allthough a formal GLP statement is not part of the report, the experiment was subjected to Quality Assurance Inspections (QAU statement is included).
11.1	**GEP**	not applicable
11.2	**Type of facility (official or officially recognised)**	[redacted]
11.3	**Justification**	not applicable
12.	**Test System**	Salmonella typhimurium: TA 98, TA 100, TA 1535, TA 1537 and TA 1538 (origin: Prof.B. Ames, Berkeley, U.S.A.)

Study design:

The tests were performed with the following concentrations of the trial substance without and with microsomal activation: 20, 80, 320, 1280 and 5120 µg/plate. The substance was dissolved in DMSO. DMSO alone was used for the negative controls (the substances and vehicles used for the positive controls are indicated below). Each Petri dish contained:
- approx. 20 ml of minimum agar plus salts and glucose,
- 0.1 ml of the solution of the test substance or the vehicle and 0.1 ml of a bacterial culture (in nutrient broth, 0.8% plus 0.5% NaCl) in 2.0 ml of soft agar.

The soft agar was composed of: 100 ml of 0.6% agar solution with 0.6% NaCl and 10 ml of a solution of l-histidine, 0.5 mM and +biotin 0.5 mM. In the experiments in which the substance was metabolically activated, 0.5 ml of an activation mixture was added also.

1 ml activation mixture contained: 0.3 ml S9 fraction of liver from mice (Tif:MAGf(SPF) and 0.7 ml of a solution of co-factors. The mice were induced:
a) with Arochlor 1254, 500 mg/kg in sesame oil, i.p., one application 5 days prior to sacrifice,
b) with CGA 64'250, 320 mg/kg in CMC 2%, p.o., one daily application on seven consecutive days; the animals were sacrificed 24 hours after the last administration.

Positive control experiments were carried out simultaneously with the following substances:
1) for strain TA 98: daunorubicin-HCl, 5 and 10 µg/0.1 ml phosphate buffer;
2) for strain TA 100: 4-nitroquinoline-N-oxide, 0.125 and 0.25 µg/0.1 ml;
3) for strain TA 1535: N-methyl-N'-nitro-N-nitrosoguanidine, 3 and 5 µg/0.1 ml
4) for TA 1537: 9(5)aminoacridine hydrochloride monohydrate, 50 and 100 µg/0.1 ml
5) for strain TA 1538: 2-nitrofluorene (Fluka, Buchs, Switzerland), 5 and 10 µg/0.1 ml.
The activation mixture was tested with TA 1535 and cyclophosphamide, 250 µg/0.1 ml.

In the experiments without and with the addition of microsomal activation mixture three Petri dishes were prepared per strain and per group (i.e. per concentration or per control group). The plates were incubated for about 48 hours at 37 $\pm$ 1.5°C in darkness. When the colonies had been counted, the arithmetic mean was calculated.

The test substance is generally considered to be non-mutagenic if the colony count in relation to the negative control is not doubled at any concentration.

13 Findings

Cytotoxicity: At the upper concentrations a growth inhibition was noted.The test substance precipitated in the soft agar at concentrations of 1'280 µg/plate and above.

xMutagenicity test: There was no increased incidence of back mutations indicative of a mutagenic response (see tables below). Numbers in parenthesis are corrections made by RMS.

Reverse mutation assay with S. typhimurium: Experiments with Arochlor induction (mean values of two independent assays (3 plates per concentration)

S. typhimurium strain	TA 98		TA 100		TA 1535		TA 1537		TA 1538	
Metabolization	without	with	without	with	without	with	without	with	without	with
Negative control	16	30	134	82	6	9	4	10	8	12
(DMSO)	22	45	147	105	11	11	7	29	17	27(37)
CGA 64'250										
20 µg/plate	22	36	122	85	9	6	4	10	10	19
	28	44	155	120	12	12	14	20	14	26
80 µg/plate	18	40	118	84	11	12	4	9	10	19
	29	49	165	104	10	9	12	15	17	34
320 µg/plate	18	33	120	84	4	9	4	7	10	17
	28	48	160	86	15	11	9	25	16	31
1'280 µg/plate	17	31	91	73	10	11	0	7	0	12
	23	44	45	85	11	15	0	16	4	31
5'120 µg/plate	1	6	1	9	1	1	0	0	0	1
	2	2	6	22	6	2	0	1	0	2
Positive control	434[a]		656[b]		2'293[c]	308[d]	33[e]		684[f]	
	570		695		1'422	323	41		812	

[a] Daunoblastin; [b] 4-Nitroquinoline-N-oxide;
[c] N-methyl-N'nitro-N-nitroso-guanidine; [d] cyclophosphamide (100 µg/plate);
[e] 9(5)-aminoacridine (50 µg/plate), [f] 2-nitrofluorene

Reverse mutation assay with S. typhimurium: Experiments with CGA 64'250 induction (mean values of two independent assays (3 plates per concentration)

S. typhimurium strain	TA 98		TA 100		TA 1535		TA 1537		TA 1538	
Metabolization	without	with	without	with	without	with	without	with	without	with
Negative control	24	30	150	91	13	15(8)	8	11	11	9
(DMSO)	22	33	115	99	9	11(15)	5	6	7	22
CGA 64'250										
20 µg/plate	24	34	141	114	8	4	5	4	12	15
	14	32	132	99	12	10	4	6	12	18
80 µg/plate	13	36	127	104	8	6	7	12	15	19
	20	36	117	108	15	11	6	6	12	18
320 µg/plate	24	27	111	124	12	9	6	8	7	15
	16	25	121	92	10	13	7	7	7	12
1'280 µg/plate	16	31	75	97	19	9	2	8	0	11
	13	25	72	101	7	11	2	7	1	8(7)
5'120 µg/plate	2	2	7	4	2	0	0	1	0	0
	1	2	1	7	3	2	0	1	0	0
Positive control	669[a]		761[b]		1'588[c]	271[d]	34[e]		736[f]	
	311		733		951	253	56		644	

xConclusion: The slight increase in the number of back mutations observed in one experiment without metabolic activation on strain 1537 and in one experiment with metabolic activation in strain 1538 is attributed to incidental fluctuations.

Propiconazole did not induce point mutations under the conditions of this test.

14	**Statistics**	none
15 (published)	**References**	Method: B.N. Ames, J. McCann, E. Yamasaki: Methods for detecting carcinogens and mutagens with the Salmonella / mammalian-microsome mutagenicity test. Mutation Research 31, 347-364, 1975
16 data	**Unpublished**	none
x17 Indicator	**Reliability**	1

Data Protection Claim	Yes

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	25.2.2005
Materials and Methods	
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 / 26.10.1994
PP 2.504 / WM / 08.11.1994

98/8 Doc IIIA section No.	**6.6.2**	**In-vitro cytogenicity study in mammalian cells**
91/414 Annex Point addressed	**II 5.4.1 / 04**	Genotoxicity Studies - *In vitro* testing

1.2	**Title**	Chromosome studies on human lymphocytes in vitro
1.3	**Report and/or project N° Syngenta File N° (SAM)**	840025 64250 / 1576
1.4	**Lab. Report N°**	840025
1.5	**91/414 Cross Reference to original study / report**	5.4.1 / 04
1.6	**Authors**	Report: [redacted] Summary:
1.7	**Date of report**	May 10, 1984
1.8	**Published / owner**	unpublished / Syngenta Ltd. Basle / Switzerland
2.1	**Testing facility**	[redacted]
2.2	**Dates of experimental work**	January 30 to May 7, 1984
3.	**Objectives**	Evaluation of any property to induce structural chromosomal aberrations.
4.1	**Test substance**	CGA 64'250, technical grade active ingredient
4.2	**Specification**	[redacted]
4.3	**Storage stability**	The a.i. is known to be stable at room temperature.
4.4	**Stability in vehicle**	not investigated. The solutions were freshly prepared before use.
4.5	**Homogeneity in vehicle**	not applicable
4.6	**Validity**	not applicable
5	**Vehicle / solven**	DMSO; the test article was dissolved in DMSO, the final concentration of DMSO in the culture medium was 1%.
6	**Physical form**	viscous liquid
7.1	**Test method**	The study was conducted according to an in-house method.
7.2	**Justification**	The test was conducted mainly in compliance with the OECD Guideline 473.
7.3	**Copy of method**	Methodological details are outlined in the original report submitted under 5.4.1 / 04. See also the description given below at point 12.
8	**Choice of method**	The method complies with sound scientific principles.
9	**Deviations from EC-Directive 92/69 B10)**	Only one single harvest time was used.
10.1	**Certified laboratory**	yes
10.2	**Certifying authority**	Swiss Federal Department of the Interior and Intercantonal Office for the Control of Medicaments.
x10.3	**GLP**	The study was conducted under Quality Assurance in compliance with GLP standards

10.4	**Justification**	not applicable
11.1	**GEP**	not applicable
11.2 (official or officially recognised)	**Type of facility**	[redacted]
11.3	**Justification**	not applicable
12.	**Test System**	Human lymphocytes obtained from a healthy volunteers.

Study design:

A preliminary toxicity test was performed to determine the concentrations to be used in the mutagenicity assay. The concentration to be selected as the highest for the mutagenicity assay is that causing approximately 50% suppression of mitotic activity in comparison with the control after a 3-hour treatment followed by 24-hour recovery phase.

The human blood used in this experiment was obtained from a normal donor by venepuncture. The white cells were separated by density-gradient centrifugation and maintained in blood culture medium. The pre-incubation time before treatment was 46 hours. The substance was dissolved in DMS0 and applied (1:100) to the cell suspension in chromosome medium. The cells were exposed for three hours to fourteen concentrations ranging from 0.12 to 1'000 µg/ml of the test substance. After removal of the test substance, the cells were washed and incubated in chromosome medium for 24 hours. The percentages of mitotic suppression in comparison with the controls were evaluated by counting at least 1'000 cells per concentration. This preliminary toxicity test was performed with and without metabolic activation.

The concentration calculated to produce about 50% suppression of mitotic activity in comparison with the control is used as the highest in the mutagenicity experiment together with four further concentrations corresponding to factors of 0.5, 0.25, 0.125 and 0.0625.

The mutagenicity tests were carried out by treating human lymphocytes with the selected concentrations (11.25, 22.5, 45.0, 90.0 and 180 µg/ml) with and without metabolic activation. The white blood cells were prepared in the same manner as in the toxicity test. About 46 hours before exposure to the test substance, a series of Falcon flasks was seeded with human lymphocytes. Subsequently, the cells were treated for three hours, both in the presence and in the absence of rat-liver S-9 activation system, with the five preselected concentrations of the test substance, with the positive control, or with the vehicle as negative control, or remained untreated as negative control. In the experiments in which the substance was metabolically activated, 1.0 ml of an activation mixture was added to 9.0 ml of cell suspension. 1.0 ml activation mixture contained: 0.15 ml S9 fraction of liver from rats induced with Arochlor 1254 and 0.2 ml of a solution of co-factors and 0.65 ml medium. Mitomycin C 0.8 µg/ml, a mutagen not requiring S9 activation, and cyclophosphamide 10.0 µg/ml, which requires activation, were used as positive control.

After treatment, the cells were washed twice with 10 ml Hanks solution to remove the test substance, resuspended in chromosome medium and allowed to grow for 43.5 hours.

Two and a half hours prior to harvesting, the cultures were treated with Colcemide (0.4 µg/ml). The experiment was terminated by hypotonic treatment (0.075 M KCl solution) of the cells, followed by fixation (methanol:acetic acid, 3:1). Drop preparations were made by the air-drying technique. Scoring of the slides: 100 complete metaphase figures altogether from cultures of two falcon flasks in the vehicle control and in the treated groups were examined for the following aberrations:

specific aberrations: breaks, exchanges, deletions, fragments and minutes

unspecific aberrations: gaps and chromosome decay

numerical aberrations: metaphases with >2n chromosomes.

13 Findings

Cytotoxicity: An about 25% reductiuon in colony forming ability was obtained at a propiconazole concentration of 250 µg/ml. Cells exposed to 125 µg/ml remained unaffected. The doses for the main study were selected accordingly

Transformation test: The results are outlined in the following table.

Chromosome aberrations in human lymphocytes

	without microsomal activation		with microsomal activation	
	% specific aberrations	% unspecific aberrations	% specific aberrations	% unspecific aberrations
Solvent control (1% DMSO)	0	3	1	0
CGA 64'250				
11.25 µg/ml	0	2	0	0
22.5 µg/ml	1	1	0	0
45 µg/ml	0	2	1	1
90 µg/ml	0	2	1	1
**180 µg/ml	0	3	0	0
Positive control*	27	13	30	2

* Without metabolic activation: Mitomycin C
With metabolic activation: Cyclophosphamide
** Reduced number of cells due to cytotoxicity

Conclusion: No evidence of a clastogenic or aneugenic effect of propiconazole was observed under the conditions of this test.

14 Statistics none

15 (published) References H.J. Evans and M.L. O'Riordan: Human peripheral blood lymphocytes for the analysis of chromosome aberrations in mutagen tests. Mutation Res. 31, 135-148, (1975).

16 data Unpublished none

x17 Indicator Reliability 1

Data Protection Claim	Yes

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	28.2.2005
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	