Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	18.7.2005
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*

98/8 Doc IIIA section No.	**6.8.1/02**	**Teratogenicity test**
Annex Point addressed	**II 5.6.2 / 02**	Developmental toxicity studies

1.2	**Title**	A modified teratology (Segment II) study in albino rats with CGA 64'250
1.3	**Report and/or project N° Syngenta File N° (SAM)**	86189 64250 / 1587
1.4	**Lab. Report N°**	MIN 862244
1.5	**91/414 Cross Reference to original study / report**	The study was conducted to confirm equivocal results obtained in a previous study (MIN 852148) reported under the point 5.6.2 /01.
1.6	**Authors**	Report: [redacted] Summary: [redacted]
1.7	**Date of report**	February 6, 1987
1.8	**Published / owner**	unpublished / SYNGENTA Ltd. Basle / Switzerland
2.1	**Testing facility**	[redacted]
2.2	**Dates of experimental work**	July 7 to August 8, 1986
3.	**Objectives**	Confirmation of equivocal results (cleft palate) observed in the main study reported under 5.6.2 / 01.
4.1	**Test substance**	CGA 64'250, technical grade active ingredient
4.2	**Specification**	[redacted]
4.3	**Storage stability**	confirmed. Dose solutions were stable at room temperature for 26 days.
4.4	**Stability in vehicle**	confirmed, see above.
4.5	**Homogeneity in vehicle**	not applicable
4.6	**Validity**	Analyses were made using a validated HPLC standard method.
5	**Vehicle / solven**	3% aqueous corn starch solution containing 0.5% Tween 80.
6	**Physical form**	viscous liquid
7.1	**Test method**	The study was conducted following FIFRA Subdiv. F, § 83-3.
7.2	**Justification**	Generally acceptable standard method, modified to fulfill the purpose of the study.
7.3	**Copy of method**	Methodological details are part of the original report submitted under 5.6.2 / 02
8	**Choice of method**	Standard method according to Guideline requirements.
9	**Deviations from EC-Directive 87/302**	Only one dose level was tested repeating the top dose level administered in the previous study. The number of animals used exceeded basic Guideline requirements.
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

12 Test system

Animal species: Rat, strain Crl:COBS CD strain
Source: [redacted]
Dose levels: 0 and 300 mg/kg
Group size: 200 females (for mating, 199 males were used).
Age/weight: Young adult, 206-305 g (females)
Administration: Oral by gastric intubation
Study duration: Days 6 to 15 of gestation
General study
Design: Daily treatment (10 ml/kg) on days 6 to 15 of gestation.
Mortality: Twice daily
Clinical signs: Daily
Body weight: Recorded on days 0, 6, 8, 12 and 20, prior to sacrifice
Food consumption: Recorded once for days 0-6 and daily thereafter
Laparohysterectomy: Dams were necropsied on day 20 of presumed gestation. Uteri were weighed and corpora lutea, live and dead fetuses and resorption sites were counted.
Fetal examination: Viable fetuses were weighed and examined for gross abnormalities. All fetuses were carefully checked for cleft palate.
Maternal examination: All dams were examined for gross pathological changes.

13 Findings

Mortality: Two unscheduled death in the treated group were attributed to test article toxicity. One additional dam died due to intubation error and one dam delivered prematurely and was subsequently sacrificed.

Clinical signs: The top dose group females showed coma, sedation, ataxia, salivation, abnormal positions, laboured respiration, ptosis and lacrimation during the treatment period.
After the adaptation of the high dose to 300 mg/kg, no more clinical signs were noted.

Body weight: A reduced body weight gain was noted in the treated group during days 6 to 16 of gestation. Also the absolute body weights were significantly lower from day 8 of gestation onwards and were still below control values at terminal sacrifice.

Food consumption: The food consumption was reduced during the treatment period in the treated group.

Fetal weights: Fetal weights were clearly reduced in both, males and females, in the treated group.

Reproductive parameters: The number of viable fetuses was reduced in the treated group. Other parameters of reproduction remained unaffected. The following table gives a survey on the findings:

Survey on reproductive parameters in rats

Parameter	0 mg/kg	300 mg/kg
Animals successfully mated	178	189
No. Pregnant	155	161
Mean No. Corpora Lutea	16.93	17.01
Mean No. Implantation Sites	14.50	14.21
Mean No. Early Resorptions	0.8	1.0
Mean No. Late Resorptions	0.1	0.1
Mean No. Resorptions	0.81	1.15
Mean No. Live Fetuses	13.69	13.06
Mean No. Dead Fetuses	0.0	0.0
Body weight males	3.57	3.40
Body weight females	3.39	3.23

Fetal observations: Out of a total of 4'186 viable fetuses (2'122 control and 2'064 from treated dams) six individuals were found with external alformations. Four individuals from the control group showed agnathia, filamental tail (2) and multiple malformations. Two treated fetuses had cleft palate. A comparison to the spontaneous incidence in rats from the same strain shows that this incidence is within the normal range (0-0.35% in untreated controls and up to 1.4% in dams showing maternal toxicity).

Incidental variations included hematomas on four control and nine treated fetuses and two pale fetuses in the treated group.

Pathology: Few macropathological changes were observed among individual dams. The incidence and distribution of the findings gave no indication for an influence of the treatment.

Conclusion: It was concluded that maternally toxic doses of propiconazole lead to reduced fetal weights. There was no evidence of teratogenicity in this study.

14	**Statistics**	Body weights, body weight gain and food consumption were analysed by one-way analysis of variance (ANOVA) with Barlett's Test for homogeneity and Dunett's Method of Multiple Comparisons between control and treated groups. Reproductive parameters (corpora lutea, implants, resorptions, viable and dead fetuses, implantation loss) were analysed by a one-sided trend test and a Chi square test. Fetal sex ratio was analysed with Mantel's test.
15 (published)	**References**	none
16 data	**Unpublished**	[redacted] Teratology (Segment II) study in rats MIN 86004 [redacted]
17 Indicator	**Reliability**	1

Data Protection Claim	Yes

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2.8.2005
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	[redacted]

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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*

98/8 Doc IIIA section No.	6.8.1/03	Teratogenicity test
Annex Point addressed	II 5.6.2 / 03	Developmental toxicity studies

1.2	Title	A teratology (Segment II) study in New Zealand White rabbits.
1.3	Report and/or project N° Syngenta File N° (SAM)	86043 64250 / 1589
1.4	Lab. Report N°	MIN 852172
1.5	91/414 Cross Reference to original study / report	5.6.2 / 03
1.6	Authors	Report: [redacted] Summary: [redacted]
1.7	Date of report	August 1, 1986
1.8	Published / owner	unpublished / SYNGENTA Ltd. Basle / Switzerland
2.1	Testing facility	[redacted]
2.2	Dates of experimental work	June 17 to July 12, 1985
3.	Objectives	Evaluation of embryo / fetal toxicity and teratogenic potential in rabbits.
4.1	Test substance	CGA 64'250, technical grade active ingredient
4.2	Specification	[redacted]
4.3	Storage stability	confirmed. Dose solutions were stable at room temperature for 10 days.
4.4	Stability in vehicle	confirmed, see above. Fresh solutions were prepared twice during the treatment period.
4.5	Homogeneity in vehicle	not applicable
4.6	Validity	Analyses were made using a validated HPLC standard method.
5	Vehicle / solven	3% aqueous corn starch solution containing 0.5% Tween 80.
6	Physical form	viscous liquid
7.1	Test method	The study was conducted following FIFRA Subdiv. F, § 83-3.
7.2	Justification	Generally acceptable standard method.
7.3	Copy of method	Methodological details are part of the original report submitted under 5.6.2 / 03
8	Choice of method	Standard method according to Guideline requirements.
9	Deviations from EC-Directive 87/302	none
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	**Type of facility (official or officially recognised)**	[redacted]
11.3	**Justification**	not applicable

12 Test system

Animal species: Rabbit, New Zealand White
Source: [redacted]
Dose levels: 0, 100, 250 and 400 mg/kg
Group size: 19 females (artificially inseminated).
Age/weight: Young adult, 3.14 - 4.15 kg
Administration: Oral by gastric intubation
Study duration: Days 7 to 19 of gestation
General study
Design: Daily treatment (5 ml/kg) on days 7 to 19 of gestation.
Mortality: Twice daily
Clinical signs: Daily
Body weight: Recorded on days 0, 7, 10, 14, 20, 24 and 29, prior to sacrifice
Food consumption: Recorded daily from day 5 to 29
Laparohysterectomy: Does were necropsied on day 29 of presumed gestation. Uteri were weighed and corpora lutea, live and dead fetuses and resorption sites were counted.
Fetal examination: Viable fetuses were weighed and examined for gross and visceral abnormalities. Thereafter, all fetuses were cleared and subjected to skeletal examination.
Maternal examination: All does were examined for gross pathological changes. In the absence of any suspect observations, histopathology was not performed.

13 Findings

Mortality: One unscheduled death occurred in both, the low and intermediate dose. The cases were attributed to intubation error. In addition, seven does (one from control, one intermediate dose and five high dose group animals) delivered prematurely or aborted and were subsequently sacrificed.

Clinical signs: The top dose group females showed soft stool and increased incidences of abortions or early deliveries.

Body weight: A reduced body weight gain was noted in the intermediate and high dose group does during the treatment period. The absolute body weights were significantly lower in the high dose group on day 20. On day 29, no significant differences were found between the corrected body weights of all groups.

Food consumption: The food consumption was reduced during the treatment period in the intermediate and high dose group. After the cessation of treatment until sacrifice food intake above control values was noted in both groups.

Fetal weights: Fetal weights were not affected by the treatment.

Reproductive parameters: The parameters of reproduction remained unaffected. An increased incidence of early resorptions was observed in the does of the high dose group, however, the number was unduly influenced by one doe with total resorptions. When this doe was excluded, no statistically significant differences were found. The following table gives a survey on the findings.

Survey on reproductive parameters in rabbits				
Parameter	Treatment mg/kg/day			
	0	100	250	400
Animals Inseminated	19	19	19	19
No. Pregnant	15	18	17	18
No. Aborted / Sacrificed	1	0	1	5
Mean No. Corpora Lutea	11.6	12.6	13.3	13.5
Mean No. Implantation Sites	8.4	9.4	10.0	9.2
Mean No. Early Resorptions	0.1	0.4	0.4	1.3
Mean No. Late Resorptions	0.6	0.4	0.3	0.8
Mean No. Resorptions	0.7	0.7	0.7	2.1
Mean No. Live Fetuses	7.2	8.6	8.7	7.2
Mean No. Dead Fetuses	0.4	0.1	0.6	0.0
Body weight males	43.0	44.4	42.8	42.8
Body weight females	44.2	43.1	41.1	43.2

Fetal observations: Out of a total of 470 viable fetuses were examined for external alformations. One individual from the intermediate dose group showed cleft lip and umbilical hernia. In the absence of any dose relation, the finding was considered to be incidental.

Visceral variations were observed in five fetuses from all groups. Various skeletal variations were found in all groups, which were obviously spontaneous in nature. The only exception was a statistically significant increase in the incidence of fully formed 13th ribs, which was observed in the high dose group fetuses. The finding was considered to be a consequence of maternal toxicity and not a direct, fetotoxic response.

Pathology: Few macropathological changes were observed among individual does. The incidence and distribution of the findings gave no indication for an influence of the treatment.

NOEL: The NOEL was 100 mg/kg for the does and 250 mg/kg for the fetuses. There was no evidence of a teratogenic potential of propiconazole.

14	**Statistics**	Body weights, body weight gain and food consumption were analysed by one-way analysis of variance (ANOVA) with Barlett's Test for homogeneity and Dunett's Method of Multiple Comparisons between control and treated groups. Reproductive parameters (corpora lutea, implants, resorptions, viable and dead fetuses, implantation loss) were analysed by a one-sided trend test and a Chi square test. Fetal sex ratio was analysed with Mantel's 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	2.8.2005
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*

98/8 Doc IIIA section No.	6.8.2	Two generations reproduction study
Annex	II	Multigeneration studies
Point addressed	5.6.1 / 01	

1.2	Title	Two generation reproduction study in albino rats with CGA 64'250 technical.
1.3	Report and/or project N° Syngenta File N° (SAM)	450-1202 64250 / 1591
1.4	Lab. Report N°	450-1202
1.5	91/414 Cross Reference to original study / report	5.6.1 / 01
1.6	Authors	Report: [redacted] Summary: [redacted]
1.7	Date of report	March 12, 1985
1.8	Published / owner	unpublished / SYNGENTA Ltd. Basle / Switzerland
2.1	Testing facility	[redacted]
2.2	Dates of experimental work	March 1, 1983 to May 31, 1984
3.	Objectives	Investigation of potential effects on growth, reproduction and offspring over two generations.
4.1	Test substance	CGA 64'250, technical grade active ingredient
4.2	Specification	[redacted]
4.3	Storage stability	confirmed. The test article is known to be stable at room temperature.
4.4	Stability in vehicle	confirmed. Fresh diets were prepared weekly. The stability was checked prior to the initiation of the study and thereafter at monthly intervals.
4.5	Homogeneity in vehicle	confirmed. Analyses of content, stability and homogeneity were conducted in monthly intervals.
4.6	Validity	Analyses were made using a validated standard method.
5	Vehicle / solven	The test article was admixed to the standard diet of the rats.
6	Physical form	viscous liquid
7.1	Test method	The study was conducted according to draft Guidelines of U.S: FIFRA Subdiv. F, § 83-4 and OECD Guideline 416.
7.2	Justification	The final Guidelines were not yet released when the study was conducted.
7.3	Copy of method	Methodological details are part of the original report submitted under 5.6.1 / 01
8	Choice of method	Standard method according to Guideline requirements.
9	Deviations from EC-Directive 87/302	none
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	**Type of facility (official or officially recognised)**	[redacted]
11.3	**Justification**	not applicable

12 Test system

Animal species: Rat, Charles River CD strain
Source: Charles River Breeding Laboratories Inc., Portage MI, U.S.A.
Dose levels: 0, 100, 500 and 2'500 ppm (= mg/kg diet)
Group size: 15 males and 30 females
Age/weight: 35 days at the start of the treatment (mean initial weight of females108.4 g
Administration: Admixture to the diet
Study duration: Continuous treatment over 12 weeks premating and thereafter over two generations. Two litters were generated in both generations. The F2 generation was bred using the second F1 litter.
Observations:
Mortality: Twice daily
Clinical signs: Twice daily
Body weight: Weekly
Food consumption: Weekly
Reproductive parameters:
Mating index, fertility index, gestation index, female fertility index and male fertility index were calculated.
Post mortem examinations:
All parental animals were examined for gross pathological changes. Organ weights of brain, ovaries and testes were measured.
From the offspring, 10 males and 10 females were randomly selected from each dose group for gross pathologic examination. Histopathology was confined to liver, reproductive organs and gross changes.

13 Findings

Mortality: Four F0 generation parental animals died or were sacrificed in a moribund condition: a 0 ppm male was sacrificed in a moribund condition during the Flb mating trials; a 100 ppm female was found dead during the pre-mating period; a 500 ppm female was found dead during the rest period between the Fla ard Flb litters; and a 2'500 ppm female was found dead during parturition of her Flb litter. During the second generation, a 500 ppm male was sacrificed in a moribund condition during the F2b mating trials (apparently the result of a cage injury) and two 2'500 ppm females died during parturition of their F2a litters (one as found dead and one was sacrificed in a moribund condition). The remaining parental animals (F0 and F1 generation) survived to final sacrifice.

Clinical signs: No consistent antemortem observations were noted which appeared to be the result the treatment.

Body weight: During the F0 generation, body weight data obtained for the treated males did not reveal any reductions which were considered to be the result of CGA 64'250 ingestion. During the F1 generation the 2'500 ppm males exhibited reduced body weight when compared to the control males. All other body weight data obtained for the treated F1 parental males were comparable to the concurrent control males. F0 and F1 parental females fed diets containing 2'500 ppm exhibited reduced body weights throughout their respective generations. In addition, the pre-mating and overall weight gains for the F0 and F1 2'500 ppm females were decreased when compared to the concurrent control females. The F1 generation females fed diets containing 500 ppm showed reductions during pre-mating when compared to the control females. No other significant body weight reductions were noted.

During the Fla litter, progeny obtained from dams exposed to 2'500 ppm exhibited reduced body weights in comparison to the control progeny on lactation days 4, 7, 14, and 21. Statistical evaluations, utilizing the individual progeny body weight data, revealed these reductions to be statistically significant when compared to the control progeny; statistical evaluations utilizing the mean litter weight data, revealed significant reductions in comparison to the control progeny beginning at lactation day 7 and continuing through weaning (lactation day 21). Body weight data obtained for the 2'500 ppm Flb progeny were reduced in comparison to the control progeny on lactation days 14 and 21. Statistically significant body weight reductions were noted for the 2'500 ppm Flb progeny at lactation day 14 (analyses utilizing individual body weight data) and day 21 (analyses utilizing individual and mean litter weight data). During the F2a litter, progeny obtained from dams exposed to 2'500 ppm exhibited statistically reduced body weights in comparison to the control progeny on lactation days 4, 7, 14 and 21 utilizing the individual progeny body weight data. Statistical evaluations utilizing the mean litter weight data, revealed significant reductions for this group in comparison to the control progeny beginning at lactation day 7 and continuing through weaning (lactation day 21). Body weight data obtained for the 2'500 ppm F2b progeny were statistically reduced in comparison~to the control progeny

on lactation days 0 through 21 (utilizing individual body weight data) and on lactation days 4 through 21 (utilizing mean litter weight data). Body weight data obtained for the 100 and the 500 ppm progeny did not reveal any consistent alterations which appeared to be a direct result of the test article.

Food intake: F0 generation males fed diets containing 2'500 ppm exhibited reduced food intake at weeks 1 and 7 of the F0 pre-mating period: F1 generation males fed diets containing 2'500 ppm exhibited reduced food intake at weeks 2, 6 and 10 of the pre-mating period. All other food consumption data obtained for parental males during both generations were comparable to the control males during the pre-mating periods. Food consumption values obtained for the 2'500 ppm F0 and F1 parental females were reduced in comparison to the control females. Food consumption data obtained for the 100 and 500 ppm females were considered to be comparable to the control females.

Reproduction: Reproductive indices calculated for the groups of rats fed CGA 64'250 were comparable to the concurrent control qroups.

Vaginal discharges were noted either during gestation or lactation of the F0 generation for 3 control (0 ppm), 1 low (100 ppm), 1 intermediate (500 ppm), and 5 high dose group females. One control and 1 F1 female resorbed their Flb litters and 2 high dose females resorbed their Fla litters. In addition, during the Flb litter a high dose group female was found dead on lactation day 1 after delivering 14 viable and 2 stillborn pups.

During the F1 generation, vaginal discharges were noted either during gestation or lactation of the F1 generation for 3 control (0 ppm), 2 low (100 ppm), 2 intermediate (500 ppm) and 3 high dose group (2'500 ppm) females. One female from each of the control, low and intermediate dose groups resorbed their F2a litters and 1 control, 2 low and 2 intermediate dose group females resorbed their F2b litters. On lactation days 0 and 1 of the F2b litter, a high dose group female exhibited pale eyes, ears, and appendages, was listless (day 0), had dried brown substance on fur (perianal). This female delivered a single pup which was cannibalized and still exhibited a vaginal discharge (tan) on lactation day 3 (3 days post parturition). In addition, during the F2a litter a high dose group female was found dead after delivering 6 viable pups and another female from the same group was sacrificed in a moribund condition on lactation day 1 after delivering 4 viable, 2 stillborn and 1 cannibalized pups.

Pup survival: Delivery and population data obtained for the groups of dams exposed to CGA 64'250 were comparable to the control dams during both the Fla and Flb litters. During the F2a litter, the numbers of pups, delivered viable and surviving to lactation day 4 were statistically reduced for the 2'500 ppm dams when compared to the control dams. Statistically significant reductions were also noted for this group of dams during the F2b litter for progeny surviving to lactation days 7, 14 and 21. No other significant differences were noted for delivery and population data during the F2a and F2b litters.

Calculated indices of progeny survival were considered to be comparable for treated and control groups during the Fla and Flb litters. During the F2b litter, progeny survival indices at lactation days 7, 14 and 21 were statistically reduced for the 2'500 ppm group dams. No other significant differences were noted for progeny survival during the F2a and F2b litters.

Malformations: Examinations of progeny structural development did not reveal any aberrant findings which were considered to be related to CGA-64250 exposure.

Organ weights: Statistical evaluation of the organ weight data obtained for F0 generation animals revealed the brain to body weight data obtained for the 2'500 ppm parental females was increased when compared to control females and significant reductions in mean final body weight, brain weight, and testes with epididymides weight and a significant increase in their brain to body weight ratio for the 2'500 ppm Fla male progeny. During the F1 generation, the brain to body weight data obtained for the 2'500 ppm parental females was increased when compared to control females. When compared to the control males, the 2'500 ppm F2a males exhibited significant reductions in mean final body weight, the testes with epididymides weight, and the testes with epididymides to brain weight ratio and a significant increase in their brain to body weight ratio. Mean final body weight data obtained for the 2'500 ppm F2a female progeny were somewhat less than the control females, however, no statistically significant differences were noted. The 2'500 ppm F2b male and female progeny exhibited significant reductions in mean final body weights. A significant increase in the brain to body weight ratio was noted for the 2'500 ppm F2b males and a significant reduction in brain weight was noted for the 2'500 ppm F2b females. No other statistically significant differences were noted in organ weight data obtained for the CGA 64'250 animals when compared to their concurrent control.

Necropsy: Gross pathologic examination of the parental animals from both generations (sacrifice, found dead, moribund sacrifice) revealed no untoward findings which appeared to be the result of CGA 64'250 ingestion. Necropsy examination conducted upon sacrificed progeny and progeny whicn died during the lactation period revealed no untoward findings which were considered the result of CGA 64'250 exposure.

Histopathology: The results of the microscopic examinations revealed the exposure of male and female albino rats to 100, 500 or 2'500 ppm of CGA 64'250 in the diet during gestation and for two reproductive cycles did not produce any changes in the reproductive tract that appear to be treatment-related. Swelling of hepatocytes in areas of the liver, diagnosed as cellular swelling, was found in the liver of the male and female F0, Flb, F1 and F2b rats and appears to be due to the administration of CGA 64'250. The incidence of this lesion was significantly increased at 500 and 2'500 ppm in the F0 and F1 parents and at 2'500 ppm in the Flb and F2b weanlings. The incidence of clear-cell change in the liver was also increased for at least one group and one sex of rats at both the 500 and 2'500 ppm levels. No other lesions found in this study were considered treatment-related.

NOEL: Based on histopathological liver changes, the NOEL was 100 ppm in this study. No effects on reproduction and post natal development were noted at a dietary concentration of 500 ppm CGA 64'250.

14	**Statistics**	Body weights and food consumption were analysed by analysis of variance (ANOVA). Significant differences were further analysed using multiple comparison methods. Organ weights were analysed Kruksal-Wallis analyses and a Chi square or Fisher's exact test, as appropriate.
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	2.8.2005
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*

98/8 Doc IIIA section No.	6.9	Neurotoxicity studies

[redacted]

[redacted]

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	4.8.2005
Conclusion	
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.	6.10/01	Mechanistic study - any studies necessary to clarify effects reported in toxicity studies

1.2	Title	CGA64250 tech. (Propiconazole). Effects on biochemical parameters in the liver following administration to male mice
1.3	Report and/or project N° Syngenta File N° (SAM)	CB 97/22 64250 / 3359
1.4	Lab. Report N°	CB 97/22
1.5	91/414 Cross Reference to original study / report	5.8/01
1.6	Authors	Report: [redacted]
1.7	Date of report	07.04.1998
1.8	Published / owner	unpublished / SYNGENTA Ltd. Basle / Switzerland
2.1	Testing facility	[redacted]
2.2	Dates of experimental work	June 25, 1997 to November 25, 1997 (experimental)
3.	Objectives	To phenotype liver enzyme induction in male CD-1 mice at doses of CGA 62450 that induced liver tumours in previous onco studies
4.1	Test substance	CGA 64'250, technical grade active ingredient
4.2	Specification	[redacted]
4.3	Storage stability	Stable at room temperature
4.4	Stability in vehicle	The test compound (and the reference substance, Phenobarbital) were mixed in diet. The compounds in diet were considered stable for the duration o fthe test
4.5	Homogeneity in vehicle	Acceptable
4.6	Validity	Analyses were made using a validated HPLC with UV detection.
5	Vehicle / solven	Pelleted diet (NAFAG 8900 FOR GLP, Nafag, Gossau SG, Switzerland).
6	Physical form	CGA 62450 is a viscous liquid
7.1	Test method	Supplementary investigative study.
7.2	Justification	Supplementary investigative study.
7.3	Copy of method	Methodological details are part of the original report submitted
8	Choice of method	Supplementary investigative study.
9	Deviations from EC-Directive 87/302	Not applicable
10.1	Certified laboratory	yes
10.2	Certifying authority	Swiss Federal Department of the Interior and Intercantonal Office for the Control of Medicaments.
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

12	**Test system**	Animal species: Male CD-1 mice (Crl:CD-1 (ICR) BR) Source: [redacted] Dose levels: 0, 850 ppm phenobarbital , 850 and 2500 ppm propiconazole Group size: 4 groups of 6 mice Age/weight: Young adult, 31.1 – 37.6 g Administration: diet Study duration: 14 days General study Design: . Clinical signs: Daily Body weight: daily Food consumption: daily At autopsy liver was taken and frozen in liquid nitrogen; samples were thawed, and homogenized in Tris/HCl buffer and microsomal and cytosolic fractions obtained by vcentifugation. Samples were analysed for protein content, microsomal cytochrome P450, EROD and PROD activity; microsomal hydroxylation of testosterone; microsomal lauric acid hydroxylation; microsomal UDP-glucuronosyltransferase; cytosolic glutathione S-transferase and microsomal epoxide hydrolase activity.

13	**Findings**
Liver wieghts	Treatment with propiconazole and Phenobarbital gave increased relative and absolute liver weights. (approx. x2 for propiconazole, x1.5 for Phenobarbital)
Protein content of liverl fractior	There was little or no impact of treatment on protein content of liver fractions
Microsomal activity	2500 ppm propiconazole induced cytochrome P450 activity by 389% of control; 850 ppm phrnobarbital induced activity by 239%
Enzyme activities	There was strongly increased activity for the microsomal mixed function oxidase reactions, total testosterone oxidation; there was a moderate induction of microsomal epoxide hydrolase as awell as a slight induction of microsomal UDP-glucuronosyltransferase and cytosolic glutathione S-transferase. Coumarin 7-hydroxylase activity was markably increased
COnclusion	The ionduction profile of CGA 64250 at 850 and 2500 ppm was qualitatively the same as that of the reference compound Phenobarbital. The effect was quantitatively the same at 850 ppm propiconazole as for 850 ppm phenobarbital. Thus CGA 64250 ia s strong Phenobarbital – type induce of liver xenobiotic metabolising enzymes

14	**Statistics**	Two-sided Dunnetts 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	4.8.2005
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	[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*

98/8 Doc IIIA section No.	6.10/02	Mechanistic study - any studies necessary to clarify effects reported in toxicity studies

1.2	**Title**	.CGA 64250 (Propiconazole) - Assessment of hepatic cell proliferation in male mice
1.3	**Report and/or project N° Syngenta File N° (SAM)**	CB 97/23 64250 / 4200
1.4	**Lab. Report N°**	CB 97/23
1.5	**91/414 Cross Reference to original study / report**	5.8/02
1.6	**Authors**	Report: [redacted]
1.7	**Date of report**	01.09.1999
1.8	**Published / owner**	unpublished / SYNGENTA Ltd. Basle / Switzerland
2.1	**Testing facility**	[redacted]
2.2	**Dates of experimental work**	June 20, 1997 to September 01, 1999 (experimental)
3.	**Objectives**	To characterise the extent and time dependence of hepatocyte proliferation after treatment of male mice with 850 or 2500 ppm propicponazole
4.1	**Test substance**	CGA 64'250, technical grade active ingredient
4.2	**Specification**	[redacted]
4.3	**Storage stability**	Stable at room temperature
4.4	**Stability in vehicle**	The test compound (and the reference substance, Phenobarbital) were mixed in diet. The compounds in diet were considered stable for the duration o f the test
4.5	**Homogeneity in vehicle**	Acceptable
4.6	**Validity**	Analyses were made using a validated HPLC with UV detection.
5	**Vehicle / solven**	Pelleted diet (NAFAG 8900 FOR GLP, Nafag, Gossau SG, Switzerland).
6	**Physical form**	CGA 62450 is a viscous liquid
7.1	**Test method**	Supplementary investigative study.
7.2	**Justification**	Supplementary investigative study.
7.3	**Copy of method**	Methodological details are part of the original report submitted
8	**Choice of method**	Supplementary investigative study.
9	**Deviations from EC-Directive 87/302**	Not applicable
10.1	**Certified laboratory**	yes
10.2	**Certifying authority**	Swiss Federal Department of the Interior and Intercantonal Office for the Control of Medicaments.
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
12	**Test system**	Animal species: Male CD-1 mice (Crl:CD-1 (ICR) BR) Source: [redacted] Dose levels: 0, 850 ppm phenobarbital , 850 and 2500 ppm propiconazole Group size: groups of 5 mice received 0, 850 or 2500 ppm propiconazole for between 1-60 days. Additional groups of 5 mice received 850 ppm Phenobarbital in the diet for the same time periods. Age/weight: Male Young adult, 31.2 – 40 g Administration: diet Study duration: 1-60 days General study Design: . Clinical signs: Daily Body weight: daily Food consumption: daily At autopsy At designated times (1, 2, 3, 4, 7, 14, 28 and 60 days) animals were killed and livers taken for subsequent bromodeoxyuridine-based immunohistochemical cell proliferation analysis (BrdU).and routine histopathological examination.

13 Findings

Liver weights	Rapid and sustained increased in absolute and relative liver weights were observed with treatment of both test and reference samples. Maximum severity was reached at 3 days for the 850ppm propiconazole group (147% control); 14 days with 2500ppm propiconazole (241%) and 4 days with 850ppm Phenobarbital (175%).
Histopathology	Hepatocellular hypertrophy was see in all treated groups with a time related increase in severity. The hypertrophy with propiconazole was characterised most prominently in centrilobular/midzonal hepatocytes in all lobular compartments, whereas the Phenobarbital-induced hypertrophy was almost exclusively in the centilobular/midzonal hepatocytes. The incidence and severity of necrosis showed a gradual time and/or dose related increase with propiconazole of Phenobarbital treated animals. An increase in hepatocellular mitotic activity was observed with propiconazole at both doses, as well as with Phenobarbital; a maximal activity was noted at day 2, but some activity lasted for up to 28 days. Cytoplasmic vacuolation was seen during the first week of treatment, and persisted with moderate to marked severity at 2500ppm propiconazole. Effects in other groups was much less marked.
BrdU	Treatment with propiconazole and Phenobarbital resulted in a rapid and steep increase in the mean BrdU index during the first few days, with a rapid decline back to control values after dat 7 (low dose propiconazole) or to slightly above controls for the high dose propiconazole and Phenobarbital doses.
Conclusion	Treatment of male mice with propiconazole at 850 or 2500 ppm propiconazole for up to 60 days resulted in a prominent, time and dose-related hepatomegaly. This enlargement was die to a sharp and transient induction of hepatocellular proliferation and hypertrophy. Other treatment related changes included hepatocellualr cytoplasmic vacuolation at 2500 ppm and a dose-related hepatocellular necrosis. From these results, propiconazole can be regarded as a Phenobarbital-like mitogen in the mouse liver

14	**Statistics**	Two-sided Dunnetts test, Mann-Whitney Rank Tests, Wilcoxon 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	5.8.2005
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*

98/8 Doc IIIA section No.	6.10/03	Mechanistic study - any studies necessary to clarify effects reported in toxicity studies
91/414 Annex Point addressed	II 5.8.6 / 01	Studies on tumour promotion

1.2	Title	Promotion study with CGA 64'250
1.3	Report and/or project N° Syngenta File N° (SAM)	834015 64250 / 1518
1.4	Lab. Report N°	834015
1.5	91/414 Cross Reference to original study / report	5.8.6 / 01
1.6	Authors	Report: [redacted] Summary: [redacted]
1.7	Date of report	October 1, 1984
1.8	Published / owner	unpublished / SYNGENTA Ltd. Basle / Switzerland
2.1	Testing facility	[redacted]
2.2	Dates of experimental work	August 23 to November 16, 1983
3.	Objectives	To determine the influence of propiconazole on formation of proliferative changes in the rat liver. The "baby rat" model was chosen as the test system.
4.1	Test substance	CGA 64'250, technical grade active ingredient
4.2	Specification	[redacted]
4.3	Storage stability	confirmed.
4.4	Stability in vehicle	Confirmed, diet preparations were analysed for content and homogeneity twice during the study period.
4.5	Homogeneity in vehicle	confirmed, see above.
4.6	Validity	Analyses were made using a validated standard method.
5	Vehicle / solven	The test substance was admixed to the standard diet of the rats.
6	Physical form	viscous liquid
7.1	Test method	Non-standard study conducted according to an in-house method.
7.2	Justification	The study was conducted according to sound scientific principles.
7.3	Copy of method	Methodological details are part of the original report submitted under 5.8.6 / 01 see also point 15 below.
8	Choice of method	The approach chosen is in accordance with an appropriate, published method.
9	Deviations from EC-Directive 87/302	not applicable
10.1	Certified laboratory	no
10.2	Certifying authority	not applicable
10.3	GLP	no

10.4	**Justification**	GLP regulations were not yet introduced at the time when the study was conducted.
11.1	**GEP**	not applicable
11.2	**Type of facility (official or officially recognised)**	[redacted]
11.3	**Justification**	not applicable

12 Test system

Animal species: Rat, strain Tif:RAIf
Source: [redacted]
Dose levels: 0 and 2'000 ppm (= mg/kg feed) propiconazole.
500 ppm phenobarbital was used as positive control.
Group size: 5 males and 5 females per dose group and sacrifice time.
Age/weight: 3 weeks old rats pretreated with N-nitrosodiethylamine 24 hours after birth.
Administration: Admixture to the diet
Study duration: 56 days. Interim sacrifices after 14 and 28 days.
General study design:
The animals were allocated as follows to treatment and control groups:

Group	Pretreatment Day 1 *post partum*	Dietary treatment after weaning	Group size and duration of treatment
1 2 3	vehicle control (0.05 ml/kg 0.9% NaCl) i.p.	control diet 500 ppm phenobarbital 2'000 ppm CGA 64'250	5 males + 5 females sacrificed after 14, 28 and 56 days of dietary treatment
4 5 6	15 mg/kg N- nitrosodietyl- amine i.p.	control diet 500 ppm phenobarbital 2'000 ppm CGA 64'250	

Mortality: Twice daily
Clinical signs: Daily
Body weight: Recorded on days 1, 3, 7, 15, 21, 28, 35, 41, 49 and 56
Food consumption: Weekly
Post mortem examinations:
Liver weights were recorded and liver sections were examined for histopathologial changes using HE and periodic acid Schliff stains. The GGT activity was determined by enzyme histochemic methods. The number and size of GGT positive foci was recorded using a digitizing tablet and a microcomputer.

13 Findings

Mortality: No mortality occurred.
Body weight: No significant differences were noted in the body weight development of the groups.
Food consumption: All animals consumed a similar amount of food.
Liver changes: The observations are outlined in the following table:

Group (n = 5)		Liver to body weight ratio (rel. to controls) 14 days	28 days	56 days	Total number of g-GT positive foci 14 days	28days	56 days
Males	1	100 %	100 %	100 %	0	1	0
	2	108 %	119 %	120 %	0	53	11
	3	107 %	132 %	134 %	0	142	422
	4	88 %	96 %	109 %	55	103	121
	5	110 %	120 %	124 %	493	367	613
	6	118 %	116 %	126 %	552	382	1'178
Females	1	100 %	100 %	100 %	14	15	38
	2	123 %	109 %	108 %	0	69	34
	3	126 %	120 %	124 %	143	165	244
	4	101 %	100 %	103 %	179	71	198
	5	127 %	115 %	124 %	612	284	660
	6	122 %	126 %	135 %	488	516	1'189

In comparison to the untreated control animals, treatment with CGA 64'250 and with phenobarbitone resulted in clearly increased liver weights. Although the individual variation was relatively high, it was found that the phenobarbital- and the CGA 64'250-treated rats showed increased incidences of preneoplastic foci. The reactions were generally more pronounced in males. Pretreatment with the nitrosamine resulted in a clearly enhanced reaction.

Foci of increased γ-GT activity were generally located at the periphery of the liver lobules. In the HE sections, many of these islands of altered hepatocytes were recognised as cell foci or mixed cell foci. No basophilic foci were observed. In addition to the focal changes, the groups treated with CGA 64'250 and phenobarbitone showed a diffuse increase in the γ-GT activity over the whole liver parenchyma.

Conclusion: Propiconazole, administered at dietary concentrations of 2'000 ppm acts as a promotor of non-neoplastic and pre-neoplastic proliferative changes in the rat liver.

14 Statistics Due to the small number of animals, statistical tests were not conducted. Generally, differences greater than 20% were regarded as possible, treatment-related effects.

15 (published) References Method:
C. Peraino, E.F. Staffeldt, V.A. Ludeman: Early appearance of histochemically altered hepatocyte foci and liver tumors in female rats treated with carcinogens one day after birth. Carcinogenesis 5: 463, 1981

16 data Unpublished none

17 Indicator Reliability 1

Data Protection Claim	Yes

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	5.8.2005
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	

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

98/8 Doc IIIA section No.	6.10/04	Mechanistic study - any studies necessary to clarify effects reported in toxicity studies
91/414 Annex Point addressed	II 5.8.6 / 02	Studies on tumour promotion

1.2	Title	The effect of propiconazole on drug metabolizing enzymes in the livers of male rats and mice
1.3	Report and/or project N° Syngenta File N° (SAM)	not specified 64250 / 1812
1.4	Lab. Report N°	not specified
1.5	91/414 Cross Reference to original study / report	5.8.6 / 02
1.6	Authors	Report: [redacted] Summary: [redacted]
1.7	Date of report	July 1984
1.8	Published / owner	unpublished / SYNGENTA Ltd. Basle / Switzerland
2.1	Testing facility	[redacted]
2.2	Dates of experimental work	not specified
3.	Objectives	To investigate the effect of repeated propiconazole treatment upon the hepatic metabolising enzyme system in rats and mice. Parameters associated with cell proliferation and early stages of tumor development were included.
4.1	Test substance	CGA 64'250, technical grade active ingredient
4.2	Specification	[redacted]
4.3	Storage stability	Confirmed. The active ingredient is stable at room temperature.
4.4	Stability in vehicle	Not investigated in this study. However, the dose solutions were freshly prepared every day.
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	In-house methodology suitable for the purpose of the study.
7.2	Justification	The study was conducted according to published standard methods.
7.3	Copy of method	Methodological details are part of the original report submitted under 5.8.6 / 02
8	Choice of method	The approach was chosen in accordance with appropriate, published methods.
9	Deviations from EC-Directive 87/302	not applicable
10.1	Certified laboratory	no