98/8 Doc IIIA section No.	6.7/02	Carcinogenicity study
91/414 Annex Point addressed	II 5.5 / 02	Long-term Toxicity and Carcinogenicity

1.2	Title	CGA 64'250: Potential tumorigenic and toxic effects in prolonged dietary administration to rats.
1.3 project N° Syngenta File N° (SAM)	Report and/or	789023 64250 / 1540
1.4	Lab. Report N°	CBG 193 / 8284
1.5 Reference to original study / report	91/414 Cross	5.5 / 02
1.6	Authors	Report: [redacted] Summary: [redacted]
1.7	Date of report	September 30, 1982
1.8 owner	Published /	Unpublished / Syngenta
2.1	Testing facility	[redacted]
2.2 experimental work	Dates of	First day of treatment: September 5, 1979. Terminal sacrifice completed after 107 weeks (males) or 109 weeks (females)
3.	Objectives	Investigation of long-term toxicity and potential carcinogenicity in rats
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 vehicle	Stability in	Confirmed. Fresh diets were prepared weekly. Dietary samples were analysed pretest and in 2 months intervals thereafter.
4.5 vehicle	Homogeneity in	Confirmed. Dietary samples were analysed pretest and in 2 months intervals thereafter.
4.6	Validity	Confirmed.
5	Vehicle / solven	The test substance was admixed to the powdered standard diet.
6	Physical form	viscous liquid
7.1	Test method	The study was conducted according to the OECD Guideline 453.
7.2	Justification	When the study was planned, the OECD Guidelines were available in draft form.
7.3	Copy of method	Methodological details are part of the original report submitted under 5.5 / 02
8 method	Choice of	not applicable
9 EC-Directive 87 / 302 B	Deviations from	none
10.1 laboratory	Certified	yes
10.2 authority	Certifying	U.S. EPA
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, Sprague Dawley CD
Source: [redacted]
Dose levels: 0, 100, 500 and 2'500 ppm (= mg/kg diet)
Group size: 80 males and 80 females
Age/weight: Young adult (4 weeks), mean body weight 160 - 163 g (males) and 115 - 118g (females) at the beginning of the treatment.
Administration: Oral with the diet
Study duration: 107 weeks (males) and 109 weeks (females)
General study
Design: Continuous dietary treatment over 24 months. 10 animals per sex and group were allocated to hematological examinations, 10 to clinical chemistry examinations and 10 to an interim sacrifice after 12 months of treatment.
Mortality: Twice Daily
Clinical signs: Daily for the first 4 weeks. Weekly thereafter.
Ophthalmology: Pretest and after 25, 51 and 103 weeks in all individuals from control and high dose group.
Hearing test: Same as ophthalmology.
Body weight: Weekly
Food consumption: Weekly
Water consumption: Daily during weeks 6, 13 and 24 in control and high dose groups.
Hematology: During weeks 26, 52, 78 and 103 (10 animals per sex and group)

Red blood cells

✓ Erythrocyte count (RBC)	✓ Mean corp. hemoglobin (MCH)
✓ Hemoglobin (Hb)	✓ Mean corp. Hb. conc. (MCHC)
✓ Hematocrit (Hct)	✓ Reticulocytes
✓ 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: During weeks 26, 52, 78 and 104 (10 animals per sex and group)
and
Females were additinally examined during week 33.

Electrolytes

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

Metabolites and Proteins

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

Enzymes:

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

Urinalysis: During weeks 24, 50, 76 and 102 (10 animals per sex and group)

Quantitative parameters:

✓ Urine volume	✓ pH-value
✓ Relative density	

Semiquantitative parameters:

✓ Bilirubin	✓ Ketones

✓ Blood	✓ Protein
✓ Color	✓ Urobilinogen
✓ Glucose	✓ Sediment

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

C	W	H		C	W	H	
✓	✓	✓	adrenals	✓	✓	✓	pituitary
			aorta	✓		✓	prostate
✓	✓	✓	brain				rectum
✓		✓	caecum	✓		✓	salivary gland
✓		✓	colon				
✓		✓	duodenum	✓		✓	seminal vesicles
			epididymides	✓		✓	skin
✓		✓	esophagus	✓		✓	spinal cord
✓		✓	eyes	✓	✓	✓	spleen
			femur (with joint)	✓		✓	sternum with bone marrow
			gross lesions	✓		✓	stomach
✓	✓	✓	heart	✓	✓	✓	testis
✓		✓	ileum	✓	✓	✓	thymus
✓		✓	jejunum	✓	✓	✓	thyroid/parathyroid
✓	✓	✓	kidneys	✓		✓	trachea
			lacrymal glands	✓		✓	urinary bladder
✓	✓	✓	liver	✓		✓	uterus
✓	✓	✓	lung				
✓		✓	lymph nodes				*others:*
✓		✓	mammary gland (female)	✓		✓	head with nasal cavities, tongue, nasopharynx and middle ear
✓		✓	muscle, skeletal				
✓		✓	nerve, peripheral				
✓	✓	✓	ovary				
✓		✓	pancreas				

13 Findings

Mortality: The total number of deaths occurring during the study was 30, 31, 32 and 25 in the males and 42, 36, 36 and 26 in the females of groups 0, 100, 500 and 2'500 ppm, respectively. The slightly higher survival of the high dose group animals was attributed to their lower feed intake and reduced body weight.

Clinical signs: No symptoms were noted during the study.

Ophthalmology: No treatment-related changes.

Hearing test: No treatment-related changes.

Body weight: During the first year of treatment, the body weight of the high dose group animals (m + f) remained significantly below the control values. Thereafter, the body weight gain remained below that of the untreated controls but differences attained statistical significance only in the females. The females receiving 500 ppm propiconacole were also slightly affected during the initial 26 weeks of the treatment.

Food consumption: The food consumption of the high dose group females remained consistently below the control values during the entire treatment period. From week 27 onward, this change was also apparent in the males, although to a lesser extent.

Food conversion: Over the first 26 weeks, reduced food conversion ratios were noted for both sexes treated at the high dose level and for the females treated at 500 ppm propiconazole.

Achieved intake: The time weighted average test article intake was 3.60, 18.10 and 96.46 mg/kg b.w. in the males and 4.57, 23.32 and 130.63 mg/kg in the females, respectively.

Water consumption: A slightly lower water consumption was noted in the top dose group females, which was attributed to the lower food intake.

Hematology: Occasional, slight intergroup differences were noted for several parameters. However, the changes showed no consistent trend and were considered to be of no toxicological significance.

Clinical chemistry: Higher urea nitrogen levels were noted during weeks 26, 33 (additional, non-scheduled examination) and 52 for female rats receiving 2'500 ppm propiconazole. The males showed a similar effect at week 78 only. Lower blood glucose concentrations were occasionally recorded in both sexes treated at 500 ppm and above.

Urinalysis: No treatment-related changes.

Organ weights: Interim sacrifice group: Increased liver weights were found in both sexes from the high dose group. Terminal sacrifice group: Both sexes receiving 2'500 ppm showed increased liver weights. In addition, lower adrenal weights were noted in the males treated at 500 ppm and in both sexes of the high dose group.

Macropathology: Interim sacrifice group: No treatment related changes.
Terminal sacrifice group: No treatment related changes.

Histopathology: Interim sacrifice group: No treatment related changes.
Terminal sacrifice group: The incidence of foci of enlarged liver cells was higher in the females of the high dose group than in the other groups (13 / 71 vs. 1 / 70 in the control group). In the absence of any evidence of progression to neoplasia, this finding was considered to reflect the increased liver weight and was not considered to be of toxicological significance.
The incidence and distribution of tumors showed no treatment related changes. All incidences remained within the normal tumor profile of the rat strain used. The findings are summarized in the following table.

NOEL: The NOEL was 100 ppm, equivalent to a mean daily intake of 3.60 mg/kg propiconazole in males and 4.57 mg/kg in females, respectively.

14	**Statistics**	Analysis of variance followed by Student's t-test was used for b.w., food consumption and clinical laboratory data. Analysis of organ weights was done using final body weights as covariate. When appropriate, organs weights were log transformed to stabilize variance. Group means were compared using Student's t-test and Williams' test. Differences in tumor incidence were directly compared usind chi square or exact probability calculations, if the number of tumors was not sufficiently high. Adjustments for intergroup differences in mortality patterns were effected by analysis of stratified contingency tables.
15 (published)	**References**	none
16 data	**Unpublished**	none
17 Indicator	**Reliability**	1

Data Protection Claim	Yes

NEOPLASTIC FINDINGS IN MALE MAIN AND INTERIM SACRIFICE GROUP RATS

	Control			100 ppm			500 ppm			2'500 ppm		
	D	I	T	D	I	T	D	I	T	D	I	T
Lymphoreticular system												
Reticulum cell sarcoma							1					
Myeloid leukaemia				1						1		
Lymphoid leukaemia							1					
Lymph node												
Haemangioma						1						
Mediastinum												
Thymic adenocarcinoma				1*								
Thymic squamous cell carcinoma				1*								
Lymphocytic thymoma												1
Skin												
Papilloma			2 [1m]			1						
Kerato-acanthoma			1						1	1		
Basal cell carcinoma												1
Basosquamous carcinoma				1		1						
Lipoma								2				1
Dermal fibroma				3		1						4 [1m]
Fibroma							1					2
Fibrosarcoma	2											1
Subcutis												
Lipoma			2	1	1	2			5	1		1 [m]
Fibroma	3		1	1		1	2		1	1		4
Fibrosarcoma				1			2	1		3		
Osteosarcoma				1								
Basal cell carcinoma							1					
Mammary adenoma				1								
Mammary fibro-adenoma										1		
Mammary adenocarcinoma						1			1	1		
Mammary fibroma									1			
Liver												
Benign liver cell tumour			2			1			2			1
Malignant liver cell tumour						1				1		1
Pancreas												
Islet cell adenoma	1			1		7 [1m]	2 [1m]		2	1		
Exocrine adenoma	1					1			2			1
Caecum												
Fibrosarcoma				1*								
Kidney												
Liposarcoma						1	1*					
Lungs												
Adenocarcinoma						1						
Heart												
Leiomyoma (vascular)						1						
Testes												
Interstitial cell tumour			1									
Prostate												
Adenocarcinoma							1					
Seminal vesicle												
Squamous cell carcinoma (coagulating gland)							1					
Pituitary												
Adenoma	7		4	10		6	10		6	4		7
Carcinoma										1*		
Thyroid												
Parafollicular carcinoma	2			1		4 [1*]	3 [1m]					3
Follicular carcinoma						1			11			1
Follicular adenocarcinoma							1		m			
Parathyroid												
Adenoma	1					1						
Adrenal												
Cortical adenoma	1		1									1
Cortical carcinoma						1*						
Phaeochromocytoma	2		1			1	1		4			
Brain												
Meningioma										1		
Glioma				1								1

	Control			100 ppm			500 ppm			2'500 ppm		
	D	I	T	D	I	T	D	I	T	D	I	T
Head Squamous cell carcinoma							1					
Buccal cavity Papilloma Squamous cell carcinoma			1	1								
Zymbals gland Sebaceous carcinoma Fibrosarcoma (orbit)	1*						1					
Pinna Neurolemmona Sebaceous cell carcinoma				1								1
Preputial gland Lipoma		1			1							
Tail Schwannoma Papilloma							1		1			1
Miscellaneous Fibrosarcoma (feet) Haemangiosarcoma (muscle) Lipoma (abdomen)						1	1			1		
Number of rats with tumours	**12**	**1**	**12**	**18**	**2**	**21**	**20**	**1**	**21**	**11**	**0**	**23**
Number of rats with malignant tumours	**5**	**0**	**0**	**10**	**0**	**9**	**14**	**1**	**2**	**7**	**0**	**8**
Number of rats examined	**20**	**10**	**30**	**22**	**10**	**28**	**21**	**10**	**29**	**16**	**10**	**34**

D: Rats killed or dying during the study
I: Rats killed at interim sacrifice
T: Rats killed at terminal sacrifice
M: Rats with more than one tumour of the same type
* : Metastasizing

NEOPLASTIC FINDINGS IN FEMALE MAIN AND INTERIM SACRIFICE GROUP RATS

	Control			100 ppm			500 ppm			2'500 ppm		
	D	I	T	D	I	T	D	I	T	D	I	T
Lymphoreticular system												
Reticulum cell sarcoma	1			1			1			2		
Lymphoblastic leukaemia				1								
Myeloid leukaemia										1		
Mediastinum												
Thymic adenocarcinoma				1*						1		
Skin												
Basal cell tumour							1					
Fibroma						1			1			
Fibrosarcoma							1					
Subcutis												
Lipoma			1				2					
Fibroma	1		3							1		
Fibrosarcoma				1						2 1*		
Mammary adenoma	2			1			1			1		
Mammary fibro-adenoma	18 8m	1	14 8m	14 6m		13 8m	11 8m	1	14 6m	6 2m		10 2m
Mammary adenocarcinoma	5 2m		1		1	5	6		8 1m	3		
Mammary carcinosarcoma	1*											
Mammary fibroma				1								
Liver												
Benign liver cell tumour			1			1						2
Cholangioma												1
Pancreas												
Islet cell adenoma						1	1		2			
Islet cell carcinoma	1											
Ileum												
Fibrosarcoma			1									
Stomach												
Squamous cell carcinoma												1
Kidney												
Renal lipomatous tumour	1											
Ovaries												
Tubular adenoma			2 1m			2	1		1			2 1m
Granulosa cell tumour				1								
Malignant mesothelioma												1 m
Uterus												
Leiomyosarcoma	1											
Cervix / Vagina												
Leiomyosarcoma									1			
Fibrosarcoma										1		
Pituitary												
Adenoma	16		11	12		15	17		15	6		13
Carcinoma	1*		1*	1*		1*				1*		1*
Thyroid												
Parafollicular carcinoma	1						4		2 1m			
Follicular carcinoma			1									1
Follicular adenocarcinoma												1
Adrenal												
Cortical adenoma												2
Cortical carcinoma				1*					1*			
Brain												
Glioma							1			1		
Spinal cord												
Glioma				1								
Buccal cavity												
Squamous cell carcinoma										1*		

	Control			100 ppm			500 ppm			2'500 ppm		
	D	I	T	D	I	T	D	I	T	D	I	T
Zymbals gland Squamous cell carcinoma	1											
Preputial gland Intraductal papilloma										1		
Abdomen Fibrosarcoma	1											
Miscellaneous Malignant mesothelioma							1*					
Number of rats with tumours	**23**	**1**	**18**	**25**	**1**	**21**	**25**	**1**	**22**	**16**	**0**	**24**
Number of rats with malignant tumours	**12**	**0**	**3**	**7**	**1**	**6**	**14**	**0**	**11**	**10**	**0**	**4**
Number of rats examined	**31**	**10**	**19**	**26**	**10**	**24**	**26**	**9**	**25**	**20**	**9**	**31**

D: Rats killed or dying during the study
I: Rats killed at interim sacrifice
T: Rats killed at terminal sacrifice
M: Rats with more than one tumour of the same type
* : Metastasizing

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	7.7.2005
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.	6.7/03	Carcinogenicity study
91/414 Annex Point addressed	II 5.5 / 03	Long-term Toxicity and Carcinogenicity

1.2	Title	CGA 64'250 Long-term feeding study in mice
1.3	Report and/or project N° Syngenta File N° (SAM)	CBG / 196 /81827 64250 / 1542
1.4	Lab. Report N°	CBG / 196 / 81827
1.5	91/414 Cross Reference to original study / report	5.5 / 03
1.6	Authors	Report: [redacted] Summary: [redacted]
1.7	Date of report	October 26, 1982
1.8	Published / owner	Unpublished / Syngenta
2.1	Testing facility	[redacted]
2.2	Dates of experimental work	Treatment commenced on September 7, 1979 and continued for two years.
3.	Objectives	Investigation of potential tumorigenic effects in mice after lifetime administration.
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	Confirmed. Fresh diets were prepared weekly. Dietary samples were analysed pretest and in 2 months intervals thereafter.
4.5	Homogeneity in vehicle	Confirmed. Dietary samples were analysed pretest and in 2 months intervals thereafter.
4.6	Validity	Confirmed.
5	Vehicle / solven	The test substance was admixed to the powdered standard diet.
6	Physical form	viscous liquid
7.1	Test method	The study was conducted according to the OECD Guideline 451.
7.2	Justification	When the study was planned, the OECD Guidelines were available in draft form.
7.3	Copy of method	Methodological details are part of the original report submitted under 5.5 / 03
8	Choice of method	not applicable
9	Deviations from EC-Directive 87 / 302 B	none
10.1	Certified laboratory	yes
10.2	Certifying authority	U.S. EPA

10.3	**GLP**	yes
10.4	**Justification**	not applicable

12	Test system	Animal species: Mouse, CD-1 Source: [redacted] Dose levels: 0, 100, 500, 2'500 ppm Group size: 64 males and 64 females (12 m + 12 f interim sacrifice after 1 yr) Age/weight: Young adult (4 weeks), mean weight at treatment start: 22 g (males) and 18g (females) Administration: Oral with the diet Study duration: 102 weeks (males) and 104 weeks (females). Interim sacrifice after 52 weeks. General study Design: Continuous dietary treatment over 2 years. Mortality: Twice daily Clinical signs: Twice daily Palpable masses: Weekly Body weight: Weekly Food consumption: Weekly Hematology: At weeks 50 and 102 Clinical Chemistry: At weeks 52 and 102

Hematology: During weeks 50 and 102 (10 animals per sex and group).

Red blood cells	
✓ Erythrocyte count (RBC)	✓ Mean corp. hemoglobin (MCH)
✓ Hemoglobin (Hb)	✓ Mean corp. Hb. conc. (MCHC)
✓ Hematocrit (Hct)	✓ Reticulocytes (week 102 only)
✓ 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: During weeks 52 / 53 and 102 / 104 (10 animals per sex and group before interim or terminal sacrifice)

Electrolytes	
Calcium	✓ Potassium
Chloride	✓ Sodium
✓ Phosphorus (inorganic)	
Metabolites and Proteins	
✓ Albumin	Globulin
✓ A/G ratio	✓ Glucose
✓ Bilirubin (total)	✓ Protein (total)
✓ Cholesterol	✓ Urea
✓ Uric acid	Protein electrophoresis
Enzymes:	Lactate dehydrogenase (LDH)
✓ Alanine aminotransferase (ALT)	✓ Alkaline phosphatase (ALP)
✓ Aspartate aminotransferase (AST)	γ-glutamyl transpeptidase (γ-GT)

Urine analysis: During weeks 51 and 101 (males) or 103 (females) overnight urine from 10 animals per per sex and group

Quantitative parameters:	
Urine volume	✓ pH-value
✓ Relative density	✓ Reducing substances
Semiquantitative parameters:	
	✓ Ketones
✓ Hemoglobin	✓ Protein
✓ Color	✓ Urobilinogen
✓ Glucose	✓ Bile pigments

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 plus cervix
✓	✓	✓	lung				
✓		✓	lymph nodes				*others:*
✓		✓	mammary gland (female)	✓		✓	head with nasal cavities, tongue, nasopharynx and middle ear
✓		✓	muscle, skeletal				
✓		✓	nerve, peripheral				
✓	✓	✓	ovary	✓		✓	harderian gland
✓		✓	pancreas				

13 Findings

Mortality: The total number of deaths occurring during the study was 29, 33, 32, and 41 in the males and 24, 20, 29 and 20 in the females of groups 0, 100, 500 and 2'500 ppm, respectively. In the initial 26 weeks of the study, mortality was slightly increased in the high dose group males (5 vs 0 deaths in controls). In the absence of any significant pathological findings and as survival remained similar to controls in later phases of the study, the observation was not considered to be of toxicological significance.

Clinical signs: No symptoms were noted during the study.

Body weight: The body weight development of the high dose group animals (m + f) remained significantly below the control values. Slight and transient variations in other groups were not considered to be of toxicological significance.

Food consumption: The food consumption of the high dose group animals was consistently increased throughout the entire treatment period in the males and, during week 1 to 78, also in the females. In the females, some of the difference was attributed to spillage of food.

Food conversion: A significantly increased food conversion ratio was calculated for the high dose group animals during weeks 1 to 26. Thereafter, no more calculations were done.

Achieved intake: The time weighted average test article intake was 10.04, 49.39 and 344.27 mg/kg b.w. in the males and 10.79, 55.60 and 340.26 mg/kg in the females, respectively.

Hematology: No treatment related effects were noted.

Clinical chemistry: Increased serum activities of ALAT and ASAT were noted in the high dose group males at interim and terminal sacrifice. At termination, increased ALP were found in the same group, in addition. Plasma cholesterol concentrations were reduced in males and females of the high dose group at interim sacrifice. At termination, the same parameter was elevated in the males while it was still below control values in the females. Other, minor deviations occurred but were not considered to be related to the treatment.

Urinalysis: No treatment-related changes.

Organ weights: Interim sacrifice group: Increased liver weights were found in both sexes from the high dose group and for the males treated at the 500 ppm dose level.
Terminal sacrifice group: Same findings as after 52 weeks of treatment.

Macropathology: Interim sacrifice group: Four males from the high dose group and two from the 500 ppm group had liver masses compared to a zero incidence in the untreated control group. No liver masses were seen in the females
Terminal sacrifice group: Increased incidences of liver masses were found in the males treated at 500 ppm and above (15/21 and 14 /14 vs. 10/24 in the control group) and in the high dose group females (11/32 vs. 3/28 in the controls).

Histopathology: Interim sacrifice group: Centrilobular enlargement of liver cells was noted in the males treated at 500 ppm and above. Liver tumors were found in one control male, and in 3 and 4 males treated at 500 and 2'500 ppm, respectively.
Terminal sacrifice group: Treatment related changes were confined to the liver of the high dose group animals and included:

hepatocyte enlargement, predominatly in the contrilobular area in male and females
dilatated and / or congested sinusoids
marginal vacuolation of hepatocytes in females
increased incidences of fat deposition in males and females

No treatment-related effects were found at 100 and 500 ppm.

The overall distibution of neoplastic findings is summarized in the following table. In the males of the high dose group, an increased incidence of liver tumors (benign and malignant) was noted.

NOEL: The NOEL was 100 ppm, equivalent to a mean daily intake of 10.04 mg/kg propiconazole in males and 10.79 mg/kg in females, respectively.

14	**Statistics**	Analysis of variance followed by Student's t-test was used to assess the significance of intergroup differences in food consumption, body weight and clinical chemistry. Mortality was analysed using a test for linear trends followed by a Chi-square contingency test. Analysis of organ weights was conducted using the body weight as a covariate. Where appropriate, a log transformation was conducted. Group meanse were compared using Student's t-test and Williams' test. Incidence data from histopathology were analysed by the method described by R. Pero et al. (1980).
15 (published)	**References**	R. Peto et al.: Guidelines for simple significance tests for carcinogenic effects in long-term animal experiments. Supplement 2, pp 311 - 426. In: IARC (ed.): Long-term and short term screening assays for carcinogens: A critical appraisal. IARC Monograph on the Evaluation of the Carcinogenic Risk to Humans. IARC Lyon 1980.
16 data	**Unpublished**	none
17 Indicator	**Reliability**	1

Data Protection Claim	Yes

NEOPLASTIC FINDINGS IN MALE MAIN AND INTERIM SACRIFICE GROUP MICE

	Control			100 ppm			500 ppm			2'500 ppm		
	D	I	T	D	I	T	D	I	T	D	I	T
Liver												
Benign liver cell tumour	7	1	5	2		5	3	2	5	10	1	11
Malignant liver cell tumour	8		7	5		2	7	1	7	20[1m]	3	3
Haemangioma						1			1			
Lungs												
Adenoma		2	6	2		4	1		1	1	1	
Adenocarcinoma	2		4	3		1	2		3[1m]			1
Lymphoreticular system												
Lymphosarcoma	6			5		3			1			
Reticulum cell sarcoma	2		1						1			
Spleen												
Haemangioma							1		1			
Haemangiosarcoma	1[m]											
Kidney												
Renal carcinoma							1					
Testes												
Interstitial cell adenoma							1					
Haemangioma						1						
Adrenal												
Phaeochromocytoma						1						
Stomach (glandular region)												
Anaplastic carcinoma			1									
Duodenum												
Intestinal adenocarcinoma							1					
Harderian Gland	4	1	3	1		1	1		5	2		1
Adenoma												
Skin												
Sebacous adenoma	1											
Subcutaneous Fibroma												1
Subcutaneous Fibrosarcoma	1			1		1	2			1		
Adipose tissue												
Haemangioma									1			
Rhabdomyosarcoma								1				
Number of mice with tumours	**22**	**3**	**21**	**16**		**8**	**18**	**4**	**17**	**31**	**5**	**14**
Number of mice with multiple tumours	**8**	**1**	**9**	**5**		**6**	**5**		**8**	**17**	**2**	**11**
Number of mice with malignant tumours	**16**		**12**	**14**		**3**	**15**	**2**	**9**	**20**	**3**	**4**
Number of mice examined	**29**	**11**	**24**	**33**	**11**	**20**	**30**	**11**	**21**	**41**	**9**	**14**

D: Mice killed or dying during the study
I: Mice killed at interim sacrifice
T: Mice killed at terminal sacrifice
M: Mice with metastasising tumours

NEOPLASTIC FINDINGS IN FEMALE MAIN AND INTERIM SACRIFICE GROUP MICE

	Control			100 ppm			500 ppm			2'500 ppm		
	D	I	T	D	I	T	D	I	T	D	I	T
Liver												
Benign liver cell tumour	1		3						2			5
Malignant liver cell tumour			1			1						3
Lungs												
Adenoma	1		5	2		7	2		5		1	4
Adenocarcinoma	2			2		3 [1m]	2		2	1		
Lymphoreticular system												
Lymphosarcoma	4	1	1	4		2	4		1	4	1	2
Reticulum cell sarcoma				1			3					
Myeloid leucaemia										1		
Spleen												
Haemangioma				1			1					1
Ovary												
Papillary cystadenoma	1		2			2	1		3			2
Tubular adenoma	1											1
Granulosa cell tumour												1
Uterus												
Leiomyoma			1	1		1						2
Enometrial sarcoma				1		2						1
Haemangioma							2					
Pituitary												
Adenoma						1						
Stomach												
Squamous papilloma						1						
Harderian Gland												
Adenoma						3	2		1			2
Skin / Subcutis												
Subcutaneous fibrosarcoma						1	1 [m]					
Mammary fibro-adenoma	1											
Mammary adenocarcinoma	2 [1m]		1 [m]	1 [m]			3					
Thorax												
Fibrosarcoma							1					
Number of mice with tumours	**9**	**1**	**12**	**12**		**15**	**19**		**13**	**6**	**2**	**17**
Number of mice with multiple tumours	**3**		**2**	**2**		**7**	**3**		**3**			**8**
Number of mice with malignant tumours	**8**	**1**	**3**	**9**		**8**	**13**		**3**	**6**	**1**	**6**
Number of mice examined	**24**	**12**	**28**	**20**	**11**	**33**	**29**	**11**	**24**	**20**	**12**	**32**

D: Mice killed or dying during the study
I: Mice killed at interim sacrifice
T: Mice killed at terminal sacrifice
M: Mice with metastasising tumours

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	15.7.2005
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.	**6.7/04**	**Carcinogenicity study**
91/414 Annex Point addressed	**II 5.5 / 04**	Long-term Toxicity and Carcinogenicity

1.2	**Title**	Long-term feeding study in mice with CGA 64'250 (propiconazole) HRC Report No. CGB / 196 / 81827 Reexamination of the liver tumor response in male and female mice. Pathology Report
1.3	**Report and/or project N° Syngenta File N° (SAM)**	CBG / 196 / 81827 64250 / 2032
1.4	**Lab. Report N°**	5.5 / 04
1.5	**91/414 Cross Reference to original study / report**	CBG / 196 / 81827 See Tier I Summary 5.5 /03
1.6	**Authors**	Report: [redacted] Summary:
1.7	**Date of report**	May 6, 1991
1.8	**Published / owner**	Unpublished / Syngenta
2.1	**Testing facility**	[redacted]
2.2	**Dates of experimental work**	April 15 to April 18, 1991
3.	**Objectives**	Reexamination of of all HE slides containing sections of liver from males and females were evaluated for histopathological changes. Lungs from males were examined for pulmonary metastases of hepatocellular carcinomas.
4.1	**Test substance**	see 5.5 /03
4.2	**Specification**	[redacted]
4.3	**Storage stability**	see 5.5 /03
4.4	**Stability in vehicle**	see 5.5 /03
4.5	**Homogeneity in vehicle**	see 5.5 /03
4.6	**Validity**	see 5.5 /03
5	**Vehicle / solven**	see 5.5 /03
6	**Physical form**	see 5.5 /03
7.1	**Test method**	not applicable
7.2	**Justification**	not applicable
7.3	**Copy of method**	not applicable
8	**Choice of method**	not applicable
9	**Deviations from EC-Directive 87 / 302 B**	not applicable
10.1	**Certified laboratory**	yes

10.2	**Certifying authority**	U.S. EPA
10.3	**GLP**	yes
10.4	**Justification**	not applicable
12	**Test system**	[redacted]

13 Findings

Criteria: Hepatocellular lesions were classified as either foci of cellular alteration, benign (hepatocellular adenoma) or malignant (hepatocellular carcinoma) using criteria of the U.S. National Toxicology Program:

Foci of cellular alteration:
- Localised lesions that vary in tinctorial variation from surrounding parenchyma
- Range from less than hepatic lobule to up to three or four lobules in greatest dimension
- Hepatocytes in foci merge with adjacent parenchyma without producing compression
- Subclassified as basophilic, eosinophilic clear cell or mixed types

Hepatocellular adenoma
- Usually a discrete lesion that compresses adjacent parenchyma
- Composed of well differentiated cells that may be eosinophilic, basophilic or vacuolated
- Absence of normal hepatic lobular architecture is the primary distinction between adenoma and focus of cellular alteration

Hepatocellular carcinoma
- Distinct trabecular or adenoid pattern
- Cells are poorly differentiated or anaplastic
- Histologic evidence of local invasiveness or metastasis
- Distinction between adenoma and carcinoma is relative and is based upon the degree of cytologic differentiation and the internal and external growth pattern

Histopathology: The following observations were made in the interim sacrifice group:

Interim Sacrifice	Males				Females			
Dose level (ppm)	**0**	**100**	**500**	**2'500**	**0**	**100**	**500**	**2'500**
Hepatocellular adenoma	1	0	4	3	0	0	0	0
Hepatocellular carcinoma	0	0	0	3	0	0	0	0
Hepatocyte enlargement - minimal - mild - moderate	2 2	4 2 1 1	8 3 5	9 0 1 8	0	0	0	7 5 2
Chronic inflammation - minimal - mild - moderate	1 1	0	2 2	6 3 2 1	0	0	0	0
Hepatocyte vacuolation - minimal - mild - moderate	6 4 2	2 2	4 3 1	2 2	3 2 0 1	8 8	5 4 1	10 5 5
Number examined:	11	11	11	9	11	11	11	12

An increased number of hepatocellular adenomas was diagnosed in the intermediate and high dose group males and a slight increase of adenomas and/or carcinomas in the high dose group males. All carcinomas were well differentiated. Histologic evidence of hepatotoxicity was present in males treated at 500 ppm and above and in the high dose group females. These changes consisted of hepatocellular enlargement, vacuolation, chronic inflammation and necrosis. The changes correlated with the increased serum activities of hepatocellular enzymes, which were observed during the in-life phase of the study and with the increased liver weights found in the same dose groups (see 5.5 / 03).

The following observations were made in the animals killed at terminal sacrifice and those found dead or killed for humane reasons during the course of the study:

Terminal Sacrifice + unsched. deaths	Males				Females			
Dose level (ppm)	**0**	**100**	**500**	**2'500**	**0**	**100**	**500**	**2'500**
Hepatocellular adenoma	18	11	15	35	5	0	2	8
Hepatocellular carcinoma - well differentiated - moderately well diff. - poorly differentiated	17 10 4 3	10 5 3 2	15 5 7 3	25 17 6 2	1 1	1 1	0	3 2 1
Animals with only hepatocellular Adenoma	11	7	9	22	5	0	2	6
Animals with at least one hepatocellular carcinoma	16	9	13	22	1	1	0	3
Hepatocyte enlargement - minimal - mild - moderate - moderately severe	12 4 7 1	6 3 3	31 15 14 2	45 0 18 26 1	0	0	0	36 12 17 7
Chronic inflammation - minimal - mild - moderate - moderately severe	30 12 13 5	26 11 9 6	26 17 6 3	38 11 14 12 1	30 11 14 3 2	26 10 10 5 1	17 7 10	21 13 4 4
Hepatocyte vacuolation - minimal - mild - moderate	7 4 3	5 3 2	7 5 2	19 8 11	14 11 3	11 9 2	17 10 6 1	29 13 11 5
Metastases in lungs	0	1	1	1	n.d.	n.d.	n.d.	n.d.
Number examined	53	53	51	55	52	53	53	52

Increased incidences of hepatocellular tumors were observed only in male mice treated at the high dose level of 2'500 ppm propiconazole. The maiority of the neoplasms were adenomas. Carcinomas were generally well differentiated and the number of pulmonary metastases was not increased. In females, incidences of adenomas and carcinomas remained similar in treated and untreated groups. Histologic evidence of hepatotoxicity was found in females treated at the high dose level and in males treated at 500 ppm and above. These changes correlated with blood biochemistry findings and with increased liver weights, which were detected in the same dose groups.

Conclusion: A tumor response was observed in male mice exposed to dietary concentrations of 2'500 ppm propiconazole. The incidence and the generally benign quality of the findings is what would be expected with a non-genotoxic hepatic enzyme inducer when administered at hepatotoxic doses. This high dose effect cannot be extrapolated to lower dose levels.

14	**Statistics**	none
15 (published)	**References**	Classification of hepatocellular lesions according to the National Toxicology Program: R.R. Maronpot, J.K. Haseman, G.A. Boorman, S.E. Eustis, G.N. Rao and J.E. Huff: Liver lesions in B6C3F6 mice: the National Toxicology Program, experience and position. Arch. Toxicol. Suppl, 10-26 (1987)
16 data	**Unpublished**	See 5.5 / 03
17 Indicator	**Reliability**	1

Data Protection Claim	Yes

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	15.7.2005
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.	**6.7 / 05**	**Carcinogenicity study**
91/414 Annex Point addressed	**II 5.5 / 05**	Long-term Toxicity and Carcinogenicity

1.2	**Title**	CGA 64250 18 months oncogenicity study in mice
1.3	**Report and/or project N° Syngenta File N° (SAM)**	943126 64250/3142
1.4	**Lab. Report N°**	943126
1.5	**91/414 Cross Reference to original study / report**	5.5 / 05
1.6	**Authors**	Report: [redacted]
1.7	**Date of report**	March 26, 1997
1.8	**Published / owner**	Unpublished / Syngenta
2.1	**Testing facility**	[redacted]
2.2	**Dates of experimental work**	Treatment commenced on November 2, 1994 and final sacrifice was on June 21, 1996
3.	**Objectives**	Investigation of potential tumorigenic effects in mice after lifetime administration.
4.1	**Test substance**	CGA 64250, 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**	Confirmed. Fresh diets were prepared every 2-4 weeks. Dietary samples were analysed pretest and at intervals throughout the study.
4.5	**Homogeneity in vehicle**	Confirmed. Dietary samples were analysed pretest.
4.6	**Validity**	Confirmed.
5	**Vehicle / solven**	The test substance was admixed to the powdered standard diet.
6	**Physical form**	viscous liquid
7.1	**Test method**	The study was conducted according to the OECD Guideline 451.
7.2	**Justification**	Not applicable
7.3	**Copy of method**	Methodological details are part of the original report submitted under 5.5 / 04
8	**Choice of method**	not applicable
9	**Deviations from EC-Directive 87 / 302 B**	none
10.1	**Certified laboratory**	yes
10.2	**Certifying authority**	Switzerland Federal Department of the Interior and the Intercantonal Office for the control of Medicants.
10.3	**GLP**	yes
10.4	**Justification**	not applicable

12 Test system

Animal species: Mouse, CD-1
Source: [redacted]
Dose levels: 0, 100, 500, 8500 ppm
Group size: 80 males (10 m interim sacrifice after 9 and 53 weeks; 10m for blood chemistry investigations at weeks –1, 9, 14, 53 and 79)
Age/weight: Young adult (4 weeks), mean weight at treatment start: 26.5 – 39.5g)
Administration: Oral with the diet
Study duration: 18 months.
General study
Design: Continuous dietary treatment over 18 months.
Mortality: Twice daily
Clinical signs: Twice daily
Palpable masses: Weekly
Body weight: Weekly
Food consumption: Weekly
Blood Chemistry: At weeks –1, 9, 14, 53 and 79

Clinical chemistry: During weeks –1, 9, 14, 53 and 79

- ✓ Cholesterol
- ✓ Alkaline phosphatase (ALP)
- ✓ Alanine aminotransferase (ALT)
- ✓ Aspartate aminotransferase (AST)

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
✓			Lacrimal gland	✓			urinary bladder
✓	✓	✓	liver				
✓			lung				
✓			lymph nodes				*others:*
✓			mammary gland	✓			head with nasal cavities,
✓			muscle, skeletal	✓			tongue, nasopharynx and
✓			nerve, peripheral	✓			muzzle
✓			Gall bladder	✓			zymbal gland
✓			pancreas				

13 Findings

Mortality: There were no statistically significant effects on survival. Data are based on Group 1 (carcinogenicity group assessment, only)

Control	16/50	32%
100ppm	17/50	34%
500ppm	20/50	40%
850ppm	18/50	36%

Clinical Signs There were no clinical signs or behavioural changes indicative of a treatment-related effect

Body weight: There were no differences in bodyweight during the first 3 months of the study. Between weeks 18-50, body weights were lower in the 850ppm group compared to control. Body weights in the 500ppm group were slightly decreased compared to controls.

Food Consumption Comparable for all groups

Blood Chemistry Treatment related decreases in plasma cholesterol were seen throughout the study at 500ppm and above, occasionally attaining statistical significance at 850ppm. Sorbitol dehydrogenase activity was seen in mice at 850ppm during week 9 and 14.

Organ Weights At the two interim sacrifices, and at termination, absolute and relative liver weights were increased in the 500 and 850ppm groups compared to controls.

Histopathology At the interim sacrifice at 9 weeks, hepatocellular hypertrophy was evident at 500 and 850ppm. Also at 850ppm there were fatty changes in the liver and increased necrosis and lymphohistiocytic infiltration.

At the interim sacrifice at 53 weeks, hepatocellular hypertrophy was evident at 500 and 850ppm.

At the end of the 18 month period, there was increased hepatocellular hypertrophy at 500 and 850ppm; deposition of pigment in Kupffer cells in the livers of 850ppm animals and increased incidence of foci of cellular change and hepatocellular adenomas at 850ppm.

Dose	0ppm	100ppm	500ppm	850ppm
Animals examined	50	50	50	50
Hapato. Hypertrophy	15	18	28	29
Kupffer cell pigmentation	3	5	3	11
Focus of cellular change	0	0	1	6
Hepato. Adenoma	1	0	3	10
Hepato. Carcinoma	1	3	2	2

Conclusion A treatment related increased incidence of enlarged livers, masses and nodules was noted in the 850ppm group compared to controls. Hepatocellular hypertrophy, fatty changes and necrosis was evident in the livers of 850ppm from week 9 on, and hepatocellular hypertrophy was evident at 500ppm.

The MTD was exceeded at 850ppm, based on evidence of liver toxicity at an early stage of treatment, and marked reductions on body weight.

The NOEL for oncogenicity was 500ppm

The NOAEL was 100ppm, equivalent to 11mg/kg/day

14 Statistics For each time point and parameter an univariate statistical analysis was performed; nonparametric methods (Lehmann, 1975) were applied to allow for non normal and normal distribution. Each treated group was compared to the control by Lepage's (2-sample test, and tested for trend using Jonckheere's test for ordered alternatives.

Survival analysis was performed by the regression model of Cox, 1972.

15 (published) References References are given in the report, pages 57-59

16 data Unpublished none

17 Indicator Reliability 1

Data Protection Claim	Yes

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.	**6.8.1/01**	**Teratogenicity test**
Annex Point addressed	**II 5.6.2 / 01**	Developmental toxicity studies

1.2	**Title**	Teratology (Segment II) study in rats
1.3	**Report and/or project N° Syngenta File N° (SAM)**	MIN 86004 64250 / 1586
1.4	**Lab. Report N°**	MIN 852148
1.5	**91/414 Cross Reference to original study / report**	5.6.2 / 01
1.6	**Authors**	Report: [redacted] Summary: [redacted]
1.7	**Date of report**	January 28, 1987
1.8	**Published / owner**	unpublished / SYNGENTA Ltd. Basle / Switzerland
2.1	**Testing facility**	[redacted]
2.2	**Dates of experimental work**	April 29 to May 16, 1985
3.	**Objectives**	Evaluation of embryotoxic, fetotoxic or teratogenic potential in rats.
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 6 hours and at 2-8°C for 34 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 according to 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 / 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 (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: Charles River Breeding Laboratories Inc., Portage MI, U.S.A.
Dose levels: 0, 30, 90 and 360 mg/kg. The high dose was reduced to 300 mg/kg due to severe signs of maternal toxicity.
Group size: 30 females (for mating, 15 males were used).
Age/weight: Young adult, 210-300 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: 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. One half of the fetuses was cleared for skeletal examination, the remainder was subjected to a visceral examination in accordance with standard methods.
Maternal examination: All dams were examined for gross pathological changes. Organs with changes were microscopically examined.

13 Findings

Mortality: One female from the vehicle control group was found dead on day 20.

Clinical signs: The top dose group females showed sedation, ataxia, salivation, abnormal positions and bradypnea during the first week of treatment.
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 intermediate and high dose groups during days 6 to 8 of gestation. During the remainder of the treatment period, a depressed weight development was only observed for the high dose group animals. The analysis of absolute body weights revealed no statisticaly significant differences.

Food consumption: The food consumption was reduced during the treatment period in the intermediate and the high dose group.

Fetal weights: There were no significant differences in fetal weights between treated groups and controls.

Reproductive parameters: All reproductive parameters (corpora lutea, implantations, resorptions, dead and live fetuses) remained similar in all groups. The following table gives a survey on the findings

Survey on reproductive parameters in rats				
Parameter	0 mg/kg	30 mg/kg	90 mg/kg	300 mg/kg
Animals successfully mated	24	24	24	23
No. Pregnant	23	21	22	22
Mean No. Corpora Lutea	16.9	16.7	17.3	16.5
Mean No. Implantation Sites	13.5	14.2	14.3	14.0
Mean No. Early Resorptions	1.1	0.7	0.5	1.0
Mean No. Late Resorptions	0.0	0.0	0.0	0.1
Mean No. Resorptions	1.1	0.7	0.6	1.1
Mean No. Live Fetuses	12.3	13.5	13.7	13.0
Mean No. Dead Fetuses	0.08	0.04	0.04	0.08
Body weight males	3.6	3.7	3.6	3.6
Body weight females	3.3	3.4	3.4	3.4

Fetal observations: Out of a total of 1'141 viable fetuses two individuals were found with external alformations (one intermediate group female with cleft lip and palate and one high dose group female with anasarca). Visceral examinations revealed one additional case of cleft lip in the intermediate dose group and two cases of cleft palate in the high dose group (one fetus was already reported to have anasarca at external examination).

Although incidences of cleft palate (1/302 in the intermediate dose and 2/285 in the high dose group) were not statistically significant, an influence of the treatment could not be excluded.

Visceral and skeletal examinations further revealed increased incidences of variations, which were considered to represent a slight delay in normal development probably due to maternal toxicity (short or absent renal papillae, dilated ureters, reduced ossification of ribs and sternebrae).

Pathology: Few macropathological changes were observed among individual dams from all treated groups. The histopathological examination gave no indication of a treatment-related ethiology.

NOEL: The NOEL was 30 mg/kg for both, dams and fetuses.

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 a two-sided trend test.
15 (published)	**References**	none
16 data	**Unpublished**	none
17 Indicator	**Reliability**	1

Data Protection Claim	Yes