DATA EVALUATION REPORT

CGA-354743

STUDY TYPE: SUBCHRONIC ORAL TOXICITY FEEDING - RAT [OPPTS 870.3100 (§82-1a)] MRID 44931710

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
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Prepared by

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DATA EVALUATION RECORD

STUDY TYPE: Subchronic Oral Toxicity - Rat [OPPTS 870.3100 (§82-1a)]

DP BARCODE: D260393
P.C. CODE: 108801

SUBMISSION CODE: S570059
TOX. CHEM. NO.: 188DD

TEST MATERIAL (PURITY): CGA-354743 (a.i. 98%)

SYNONYMS: Metolachlor ESA (degredate of metolachlor)

CITATION: Bachmann, M. (1999) CGA-354743: Final report. 3-month oral toxicity study in rats (Administration in food). Novartis Crop Protection AG, Toxicology, 4332 Stein, Switzerland. Study # 971142, Novartis # 1187-98. January 26, 1999. MRID 44931710. Unpublished.

SPONSOR: Novartis Crop Protection, Inc., 410 Swing Road, P.O. Box 18300, Greensboro, NC 27419.

EXECUTIVE SUMMARY: In a 90-day subchronic oral toxicity limit study (MRID 44931710), groups of 10 male and 10 female Crl: CD BR rats were given CGA-354743 (Lot/Batch # KI-5408/6, 98% a.i.) administered in the diet at concentrations of 0, 360, 1200, 6000, or 20,000 ppm. These concentrations were equivalent to 0, 25.1, 86.2, 427.0 or 1545.0 mg/kg/day for males and 0, 28.4, 98.3, 519.0 and 1685.0 mg/kg/day for females. An additional 10 male and 10 female rats were given CGA-77102 (s-Metolachlor)(Lot/Batch # P.501001, 98.5% a.i.) administered in the diet at 5000 ppm (equivalent to 429 mg/kg/day for males and 563 mg/kg/day for females). The study was designed to assess the subchronic oral toxicity of CGA-354743 technical and to compare its toxic effects with those of its parent compound, CGA-77102 technical.

No deaths or clinical signs of toxicity occurred during this study. In addition, no statistically significant changes in body weight, body weight gain, food consumption, food efficiency, ophthalmologic examination, urinalysis, or histopathology was reported for animals fed CGA-354743. Limited and sporadic statistically significant changes in hematology, clinical chemistry, water intake and organ weight data were not dose-dependent, and were of questionable toxicological and biological importance.

Dietary exposure to CGA-77102 produced a statistically significant decreased body weight gain (-20%, $p \leq 0.01$) in males during week 1 only. Females exposed to CGA-77102 showed decreased body weight gain (-19%) by week 13, but these changes were not statistically significant. The food efficiency of rats fed CGA-77102 was decreased relative to their respective

control animals. Male and female rats had increased absolute and relative liver weights. These results are consistent with a mild liver hypertrophy in females.

Based on the data presented in this study, the NOAEL is ≥20,000 ppm (1543 mg/kg/day and 1685 mg/kg/day for females) for CGA-354743. A LOAEL could not be established. At 5000 ppm (429 mg/kg/day in males and 563 mg/kg/day in females) CGA-77102 , there evidence of decreased body weight gain and food efficiency, increased absolute and relative liver weights and an increased incidence of hepatic centrilobular hypertrophy, although the effects were mild.

This subchronic oral toxicity study in rats is classified as **Acceptable/Guideline [OPPTS 870.3100 (§82-1a)]** and satisfies the guideline requirements.

COMPLIANCE: Signed and dated GLP, Quality Assurance, Data Confidentiality, and Flagging statements were provided.

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I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: CGA-354743

Description: Solid
Lot/Batch #: KI-5408/6
Purity: 98% a.i.
Stability of compound: 5 weeks at room temperature
CAS #: not reported
Structure: not available

2. Vehicle and/or positive control

none

3. Test animals

Species: Rat
Strain: Crl: CD BR
Age/weight at study initiation: males: 4 weeks, 127 -174 g; females: 4 weeks, 104 - 149 g
Source: Charles River Deutschland GmbH, Sulzfeld, Germany
Housing: Individually, Macrolon type 3 cages
Diet: Certified standard diet (NAFAG # 8900), *ad libitum*
Water: tap water, *ad libitum*

4. Environmental conditions

Temperature: 20-24°C
Humidity: 45-65%
Air changes: 16-20/hour
Photoperiod: 12 hour light/dark cycle
Acclimation period: 11 days

B. STUDY DESIGN

1. In life dates - start: 02/23/98 end: 05/29/98

2. Animal assignment

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Animals were assigned to one of 6 groups based on body weights using a computer randomization program (Table 1). Ten rats/sex/dose were used except for the control groups where 20/sex were used. Of the treated rats, four groups were given varying

concentrations of CGA-354743, and one group was fed CGA-77102 tech. (S-Metolachlor, batch # P.501001, a.i.% 98.5%). CGA-77102 was used to allow direct comparison of the toxicity to CGA-354743 (a major soil metabolite of CGA-77102).

TABLE 1. Study Design

Group	Group number	Number of animals	Dose (mg/kg/day)[a]	
			Males	Females
CGA-354743				
control	1	20 ♂/20♀	0.0	0.0
360 ppm	2	10 ♂/10♀	25.1	28.4
1200 ppm	3	10 ♂/10♀	86.2	98.3
6000 ppm	4	10 ♂/10♀	427.0	519.0
20000 ppm	5	10 ♂/10♀	1545.0	1685.0
CGA-77102				
5000 ppm	6	10 ♂/10♀	429.0	563.0

[a] Dose level (mg/kg/day) was taken from p. 43; MRID 44931710.

3. Dose selection rationale

Doses were selected by the sponsor based on previous subchronic toxicity studies with CGA-77102. The lowest dose, 360 ppm, was intended as the NOAEL, 1200 ppm to cause no or minimal adverse effects, 6000 ppm to cause minimal adverse effects, and 20,000 ppm to cause observable adverse effects with no or few fatalities. CGA-77102 was tested on an equimolar basis, comparing 5000 ppm CGA-77102 with 6000 ppm CGA-354743.

4. Test diet preparation and analysis

The appropriate amount of CGA-354743 was weighed (without adjustment for purity) and mixed with pulverized diet containing approximately 25% water. After mixing, pellets were formed and air dried. CGA-77102 (an oily liquid) was weighed and 130 g dissolved in 500 mL acetone. A premix diet was made using an aliquot of this solution added to a fixed amount of diet. The acetone was removed under vacuum at 22°C and the premix mixed with a fixed diet quantity to yield appropriate treatment concentrations. Fresh diets were prepared monthly and stored at room temperature.

Analyses were performed on all test diets used for treatment weeks 1-5 and 10 to the end of the study. Batches used for weeks 1 - 5 were analyzed for homogeneity using samples taken at the beginning, middle and end of the pelleting process. Stability analyses were performed after 5 weeks storage at room temperature from pretest preparations at 100, 1000, 10,000 and 20,000 ppm.

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Results –

Homogeneity: CGA-354743 concentrations ranged from 96.4 - 102.8% of nominal.

Stability: CGA-354743 was stable for 5 weeks at room temperature. Concentrations varied between -10.4% and +1.4% of the mean values calculated from the homogeneity determinations.

Concentration: Mean concentrations of 106%, 105%, 108%, 106% and 106% of nominal for groups 2-6, respectively, were calculated.

The analytical data was sufficient to establish that the mixing procedure was adequate and the variance between nominal and actual dosage to the animals was acceptable.

5. Statistics

Body weight, food consumption, laboratory data and organ weight data were analyzed using univariate analyses at each time point. Each treatment group was compared to the control group either by Lepage's or by Wilcoxon's two-sample test and tested for increasing or decreasing trends from control up to the respective dose group by Jonckeere's test for ordered alternatives.

C. METHODS

1. Observations

Animals were observed twice daily for mortality and moribundity.

2. Body weight

Animals were weighed at study initiation and once per week throughout the study.

3. Food consumption, compound intake and water intake

Food consumption, compound consumption and water intake were calculated weekly.

4. Blood was collected from all animals at the end of week 13 via orbital sinus puncture after overnight fasting for hematology and clinical biochemical analysis. The CHECKED (X) parameters were examined.

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a. Hematology

x	Hematocrit (HCT)*	x	Leukocyte differential count*
x	Hemoglobin (HGB)*	x	Mean corpuscular HGB (MCH)
x	Leukocyte count (WBC)*	x	Mean corpusc. HGB conc.(MCHC)
x	Erythrocyte count (RBC)*	x	Mean corpusc. volume (MCV)
x	Platelet count*		Reticulocyte count
	Blood clotting measurements*	x	Red cell volume distribution width (RDW)
x	(Thromboplastin time)	x	Hemoglobin concentration distribution width (HDW)
	(Clotting time)		Methemoglobin (metHb)
x	(Prothrombin time)		
x	(Fibrinogen)		

* Required for subchronic studies based on Subdivision F Guidelines

b. Clinical chemistry

	ELECTROLYTES		OTHER
x	Calcium*	x	Albumin*
x	Chloride*	x	Blood creatinine*
	Magnesium	x	Blood urea nitrogen*
x	Phosphorus*	x	Total Cholesterol
x	Potassium*	x	Globulins
x	Sodium*	x	Glucose*
		x	Total bilirubin
	ENZYMES	x	Total serum protein (TP)*
x	Alkaline phosphatase (ALK)	x	Triglycerides
	Cholinesterase (ChE)		Serum protein electrophores
	Creatine phosphokinase	x	A/G ratio
	Lactic acid dehydrogenase (LDH)		
x	Serum alanine amino-transferase (also SGPT)*		
x	Serum aspartate amino-transferase (also SGOT)*		
x	Gamma glutamyl transpeptidase		
	Glutamate dehydrogenase		

* Required for subchronic studies based on Subdivision F Guidelines

5. Urinalysis

Urine was collected overnight from individual rats housed in metabolism cages. The CHECKED (X) parameters were examined.

Physical/chemical examinations			
x	Volume	x	Ketones
x	Relative Density	x	Urobilinogen
x	Color	x	Bilirubin
x	pH	x	Erythrocytes
x	Protein	x	Leukocytes
x	Glucose		

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6. Ophthalmologic examination

Control and highest dose animals were examined ophthalmologically prior to dosing and during week 13. Examinations included ophthalmoscopic inspection and induction of mydriasis with Mydriaticum™.

7. Neurotoxicity screening

Neurotoxicity screening was not performed.

8. Sacrifice and pathology

Animals were sacrificed at the end of week 13 via carbon dioxide anesthesia and exsanguination following overnight fast. Necropsies were done on all animals and tissues from each animal were preserved in neutral buffered 4% formalin. After formalin fixation, tissues were embedded in paraffin, sectioned at 3-5 microns, stained with hematoxylin and eosin, and subjected to microscopic analyses. The CHECKED (X) tissues were collected and examined histologically. The (XX) organs, in addition, were weighed.

	DIGESTIVE SYSTEM		CARDIOVASC./HEMAT.		NEUROLOGIC
x	Tongue	x	Aorta*	xx	Brain*
x	Salivary glands*	xx	Heart*	x	Periph. nerve*
x	Esophagus*	x	Bone marrow*	x	Spinal cord (3 levels)[T]
x	Stomach*	x	Lymph nodes*	x	Pituitary*
x	Duodenum*	xx	Spleen*	x	Eyes (optic n.)[T]
x	Jejunum*	xx	Thymus*		
x	Ileum*				GLANDULAR
x	Cecum*		UROGENITAL	xx	Adrenal gland*
x	Colon*	xx	Kidneys*+	x	Lacrimal gland[T]
x	Rectum*	x	Urinary bladder*	x	Mammary gland[T]
xx	Liver*+	xx	Testes*+	x	Parathyroids*
x	Pancreas*	xx	Epididymides	xx	Thyroids*
		x	Prostate		
	RESPIRATORY	x	Seminal vesicle		OTHER
x	Trachea*	xx	Ovaries	x	Bone
x	Lung*	x	Uterus*	x	Skeletal muscle
x	Nose	x	Vagina	x	Skin
	Pharynx			x	All gross lesions and masses*
	Larynx			x	Harderian glands
				x	Zymbal's glands

* Required for subchronic studies based on Subdivision F Guidelines
+ Organ weight required in subchronic and chronic studies.
T = required only when toxicity or target organ

II. RESULTS

A. OBSERVATIONS

No deaths or clinical signs of toxicity were reported during the study.

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B. BODY WEIGHT AND WEIGHT GAIN

Body weight and body weight gain were not affected by CGA-354743 treatment. Dietary exposure to CGA-77102 produced a statistically significant decreased body weight gain (-20%, $p \leq 0.01$) in males during week 1 only. Females exposed to CGA-77102 showed decreased body weight gain (-19%) by week 13, but these changes were not statistically significant. Data are presented in Tables 2a and 2b.

Table 2a: Mean body weight (g) and mean body weight gain in males treated with CGA-34743 or CGA-77102

	Dose Levels (ppm)					
	CGA-354743					CGA-77102
	0	360	1200	6000	20000	5000 ppm
Mean Body Weight (g)						
Week -1	148.8 ± 10.26	150.00 ± 11.11	150.7 ± 9.47	151.6 ± 13.20	153.0 ± 12.43	149.6 ± 12.26
Week 1	208.0 ± 10.03	211.8 ± 8.61	212.7 ± 10.70	209.6 ± 15.89	210.2 ± 13.34	196.9 ± 15.49
Week 13	491.1 ± 47.69	509.4 ± 25.81	515.1 ± 38.08	498.0 ± 51.72	506.5 ± 48.80	476.0 ± 53.79
Cumulative Mean Body Weight Gain (g)						
Week 1	59.21 ± 6.68	61.81 ± 5.61	61.99 ± 5.08	58.05 ± 3.71	57.18 ± 4.64	47.30 ± 8.15*
Week 13	342.3 ± 45.89	359.4 ± 27.88	364.4 ± 40.02	346.4 ± 46.16	353.5 ± 48.63	326.5 ± 55.32

Extracted from Tables 8.7 (pages 72-75) and 8.9 (pages 82-85) of MRID 44931710

Table 2b: Mean body weight (g) and mean body weight gain in females treated with CGA-34743 or CGA-77102

	Dose Levels (ppm)					
	CGA-354743					CGA-77102
	0	360	1200	6000	20000	5000 ppm
Mean Body Weight (g)						
Week -1	124.6 ± 9.00	125.8 ± 6.02	128.0 ± 10.73	124.5 ± 10.58	124.3 ± 9.11	125.6 ± 12.19
Week 1	154.0 ± 13.48	156.5 ± 6.60	158.1 ± 13.80	156.2 ± 14.02	151.5 ± 11.19	147.4 ± 17.08
Week 13	273.0 ± 26.98	284.4 ± 25.39	269.1 ± 30.64	272.2 ± 27.18	264.6 ± 28.20	247.3 ± 34.69
Cumulative Mean Body Weight Gain (g)						
Week 1	29.34 ± 5.74	30.71 ± 4.30	30.12 ± 4.91	31.66 ± 4.36	27.21 ± 4.76	21.80 ± 6.65
Week 13	148.4 ± 21.76	158.6 ± 25.19	141.1 ± 21.06	147.6 ± 20.03	140.3 ± 23.29	121.7 ± 25.84

Extracted from Tables 8.7 (pages 76-79) and 8.9 (pages 86-89) of MRID 44931710

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C. FOOD CONSUMPTION, COMPOUND INTAKE AND WATER INTAKE

1. Food consumption

Mean food consumption (g/animal/week) and food consumption ratios (g food/kg body weight/day) in animals fed CGA-354743 were not significantly changed throughout the study.

2. Compound consumption

Achieved doses were generally close to nominal in all cases (Table 3).

TABLE 3. Mean compound consumption of CGA-354743 and CGA-77102

Group Number	Males		Females	
	Target Dietary Level mg/kg/day	Achieved Dietary Level mg/kg/day (% nominal)	Target Dietary Level mg/kg/day	Achieved Dietary Level mg/kg/day (% nominal)
Group 1	0	0	0	0
Group 2	25.1	26.6 (106%)	28.4	30.1 (106%)
Group 3	86.2	90.6 (105%)	98.3	103.0 (105%)
Group 4	427.0	461.0 (108%)	519.0	560.0 (108%)
Group 5	1545.0	1638.0 (106%)	1685.0	1786.0 (106%)
Group 6	429.0	454.0 (106%)	563.0	597.0 (106%)

Data taken from p. 43; MRID 44931710.

3. Food efficiency

Food efficiency of rats fed CGA-354743 was similar to that of control rats. The food efficiency of rats fed CGA-77102 was decreased relative to their respective control animals (Table 4).

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TABLE 4. Mean overall group food efficiency (weeks 1-13)[a]		
Treatment group	**Males**	**Females**
Group 1 - Control	13.7	8.5
Group 2 - CGA-354743	14.9	9.5
Group 3 - CGA-354743	14.7	8.5
Group 4 - CGA-354743	14.4	8.2
Group 5 - CGA-354743	13.2	8.2
Group 6 - CGA-77102	11.8	6.1

[a]Data calculated by the reviewer: $\frac{\text{Overall body weight gain (g)}}{\text{Total food consumption} \times 100}$

4. Water Intake

The water consumption of male and female rats fed 20,000 ppm CGA-354743 was statistically increased approximately 25% relative to their respective control rats throughout the study. No other significant differences in water consumption for the remaining groups was found.

D. CLINICAL PATHOLOGY

1. Hematology

Although sporadic statistically significant changes were found in certain hematological parameters, they were of little toxicological or biological relevance and were within the reference values for the laboratory. These included marginally increased counts for white blood cells, eosinophils, and lymphocytes for females receiving 6000 ppm (519 mg/kg/day) CGA-354743 and the MCV of male rats receiving 6000 ppm (427.0 mg/kg/day).

2. Clinical chemistry

Sporadic statistically significant changes for a limited number of clinical chemistry parameters were reported. These included phosphorous for males receiving 20,000 ppm (1545 mg/kg/day) and females receiving 6000 ppm (519 mg/kg/day), and urea for males receiving 20,000 ppm (1545 mg/kg/day) CGA-354743. These changes were not dose-dependent, were within historical limits for the laboratory, and of no toxicological and biological relevance.

Males fed 5000 ppm CGA-77102 had statistically significant increases of glucose and total serum protein, as well as decreases of AST and ALT activity. Female rats fed 5000 ppm CGA-77102 had statistically increased cholesterol and phosphate and

decreased total serum bilirubin. These changes in clinical chemistry parameters were within the reference values provided by the laboratory and of no toxicological or biological significance. The study report indicates that GGT values were increased in males and females. However, examination of the individual animal data shows that GGT was measured only in the GCA-77102 treated animals. Therefore, these values cannot be compared to control measurements. It appears that there is also no reference value for GGT from this laboratory, as it is listed as 0.0 for both males and females in Appendix D.

E. URINALYSIS

No treatment-related findings were reported for any group fed CGA-354743. Males rats fed 5000 ppm CGA-77102 had increased leukocytes in the urine (220/µL compared with 80/µL in control rats). The significance of this finding is unknown.

F. OPHTHALMIC EXAMINATION

Ophthalmic examination revealed no treatment-related changes.

G. SACRIFICE AND PATHOLOGY

1. Organ weight

Statistically significant changes to rats fed CGA-354743 in organ weights were limited to increased absolute brain weight of 20,000 ppm (1545 mg/kg/day) males, absolute kidney weight of 6000 ppm (519 mg/kg/day) females, and spleen weight relative to body weight of 20,000 ppm (1685 mg/kg/day) females. These increases, though statistically significant, were unrelated to dose and not of a magnitude to be toxicologically and biologically significant.

Both male and female rats fed 5,000 ppm CGA-77102 had increased liver weights relative to control animals, although the increases were not statistically significant. Likewise, the liver weight relative to body weight of male rats was increased, though not statistically. The liver to body weight ratio of female rats was statistically significant compared with control rats.

TABLE 5. Body and liver weight and liver to body weight ratios of rats fed 5000 ppm CGA-77102

Parameter	Males		Females	
	0.0 ppm	5000 ppm	0.0 ppm	5000 ppm
Body Weight	472.9 ± 45.65	461.2 ± 52.27	258.9 ± 25.86	236.1 ± 32.10
Absolute Liver Weight	19.44 ± 3.32	21.88 ± 3.76	9.853 ± 1.09	10.14 ± 1.62
Liver to Body Weight	41.02 ± 4.92	47.35 ± 4.71	38.08 ± 2.33	42.97 ± 3.83*

*$p<0.05$
Data from pp. 161-170; MRID 44931710

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2. Gross pathology

No treatment-related gross pathology findings were reported.

3. Microscopic pathology

No microscopic pathology findings were reported for rats fed CGA-354743. Four of ten female rats fed 5000 ppm CGA-77102 had minimal to slight hepatic centrilobular hypertrophy as compared to the none in the control group.

III. DISCUSSION

A. STUDY AUTHOR'S CONCLUSIONS

The study author concluded that CGA-354743 was well-tolerated up to the limit dose of 20000 ppm. The dose of 6000 ppm CGA-354743 was the NOEL and the dose of 20000 ppm is the NOAEL. (The basis for setting the NOEL/NOAEL was not given.) The dietary concentration of 5000 ppm of CGA-77102 represents the Maximum Tolerated Dose.

B. DISCUSSION

Administration of CGA-354743 in the diet to male and female Crl:CD BR rats at concentrations of 0.0, 360, 1200, 6000, or 20,000 ppm (equivalent to 0.0 25.1, 86.2, 427.0 and 1545 mg/kg/day for males and 0.0, 28.4, 98.3, 519.0 and 1685 mg/kg/day for females) for 90 days resulted in few observed effects. The highest dose tested exceeded the guideline recommended limit intake of 1000 mg/kg/day. An additional 10 rats/sex/group were administered CGA-77102 in the diet at a dose of 5000 ppm (429 mg/kg/day for males and 563 mg/kg/day for females).

All animals survived to study end and no clinical signs were reported. There were no statistically significant changes in body weight, body weight gain, food consumption, food efficiency, ophthalmoscopic examination, urinalysis, or histopathology in animals treated with CGA-354743. Dietary exposure to CGA-77102 produced a statistically significant decreased body weight gain (-20%, $p \leq 0.01$) in males during week 1 only. Females exposed to CGA-77102 showed decreased body weight gain (-19%) by week 13, but these changes were not statistically significant. The food efficiency of rats fed CGA-77102 was decreased relative to their respective control animals.

Statistically significant changes in hematologic parameters were limited to marginally increased counts for white blood cells, eosinophils, and lymphocytes of females receiving 6000 ppm (519 mg/kg/day) and the MCV of male rats receiving 6000 ppm (427.0 mg/kg/day) CGA-354743. However, these changes were not dose-dependent, were within historic reference ranges, and are not considered toxicologically or biologically relevant. Sporadic statistically significant changes in a limited number of clinical chemistry parameters were also reported. These included phosphorous for males

receiving 20,000 ppm (1545 mg/kg/day) and females receiving 6000 ppm (519 mg/kg/day), and urea for males receiving 20,000 ppm (1545 mg/kg/day) CGA-354743. These changes also were not dose-dependent, were within historical limits for the laboratory, and of no toxicological and biological relevance. Although it appeared that male and female rats fed 5000 ppm CGA-77102 had marginally increased serum GGT activity, there is some confusion about the extent of the analyses for this parameter, as discussed in Study Deficiencies. Male and female rats did have increased absolute and relative liver weights. These results are consistent with a mild liver hypertrophy observed microscopically in females. No toxicologically relevant increases of organ weights were found for rats fed CGA-345743.

The data presented in this study show that the NOAEL for CGA-354743 is ≥20,000 ppm (1545 mg/kg/day for male and 1685 mg/kg/day female rats). No LOAEL could be established. The highest dose tested for both males and females exceeded the guideline limit dose. At 5000 ppm (429 mg/kg/day in males and 563 mg/kg/day in females) CGA-77102 , there evidence of decreased body weight gain and food efficiency, increased absolute and relative liver weights and an increased incidence of hepatic centrilobular hypertrophy, although the effects were mild.

B. STUDY DEFICIENCIES

The blood chemistry summary on page 134 of MRID 44931710 lists a mean GGT values of 0.1 for group 1 (control) males. However, the individual animal data on page 270 shows values of 0.000 for all animals. In fact, based on the individual animal data, the only animals which had GGT measurements were the group 6 males and females. In addition, only 5/10 females in group 6 had values listed in the individual animal data. Section 3.6 Laboratory investigations states that laboratory investigations (hematology, blood chemistry and urine analyses) were carried out on all surviving animals at the end of the treatment period. Failure to measure GGT is not included in section 2.2 Deviations from the protocol. This irregularity should be clarified but it does not alter the final conclusions of the study.

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