7/23/2001

DATA EVALUATION REPORT

CGA-24705

STUDY TYPE: SUBCHRONIC ORAL TOXICITY - RAT [OPPTS 870.3100 (§82-1a)]
MRID 44775401

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
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Prepared by

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DATA EVALUATION RECORD

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

DP BARCODE: D254363
P.C. CODE: ~~108800~~ 108801

SUBMISSION CODE: S558712
TOX. CHEM. NO.: None

PC 108801 TEST MATERIAL (PURITY): CGA-24705 tech.(a.i. 97.7%)

SYNONYMS: Metolachlor, Alphametolachlor

CITATION: Fankhauser, H. (1999) CGA-24705 Final Report. 3-month oral toxicity study in rats (administration in food). Novartis Crop Protection AG, Toxicology, 4332 Stein, Switzerland. Study ID # 971143, Novartis # 1162-98. January 25, 1999. MRID 44775401. Unpublished.

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

EXECUTIVE SUMMARY: In a 3-month dietary toxicity study (MRID 44775401), groups of male and female Sprague-Dawley rats (20/sex for controls, 10/sex/ treated group) were given CGA-24705 (a.i. 97.7 %, Lot/Batch P.111072) administered in feed at 0, 30, 300 or 3000 ppm (equivalent to 0, 2.00, 20.2 and 210 mg/kg/day for males and 0, 2.32, 23.4 and 259 mg/kg/day for females).

No treatment-related deaths or clinical signs occurred during the study. In addition, there were no treatment-related effects on ophthalmologic parameters, water consumption, urinalysis, food efficiency or pathology in either males or females. There was no evidence of any treatment-related effect in males.

Decreased body weights were observed in females given 300 ppm and 3000 ppm CGA-24705; however, decreases in the 300 ppm group were not considered toxicologically significant due to the small magnitude of the effect. Statistically significant decreased (22%) overall body weight gains were observed in 3000 ppm females. Decreases in the 30 and 300 ppm females was not considered toxicologically significant due to the lack of statistical significance and no dose-response effect. Statistically decreased food consumption was reported in 30, 300 and 3000 ppm females during Week 1 and in the 30 and 300 ppm group throughout the study. Overall mean food consumption was statistically decreased in 30, 300 and 3000 ppm females (-11%, -11% and -12%). The toxicological effect of treatment on food consumption is questionable as there was no dose-responsive effect and food efficiency was not affected.

Changes in a number of hematologic and clinical chemistry parameters were observed in female animals at all dose levels during the study; however, the toxicological significance is questionable due to the lack of a dose-response and the small magnitude of the effect.

Statistically significant changes in absolute and relative organ weights were limited to decreased liver weight in 30 and 300 ppm females (-11 % and -12%, respectively), increased liver/body weight in 3000 ppm females (+9), and increased kidney/body weight in 30, 300 and 3000 ppm females (+9%, +11% and +13%, respectively). These effects are not considered toxicologically significant due to the small magnitude and the lack of accompanying histopathology changes.

The LOAEL for female Sprague-Dawley rats was 3000 ppm (259 mg/kg/day) based on decreased body weight and body weight gain. The NOAEL for females was 300 ppm (23.4 mg/kg/day). The LOAEL for male Sprague-Dawley rats was not established. The NOAEL for males was 3000 ppm (210 mg/kg/day).

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

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

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: CGA-24705 tech.

Description: Viscous liquid
Lot/Batch # : P. 111072
Purity: a.i. 97.7%
Stability of compound: 7 weeks at room temperature
CAS #: Not reported
Structure: Not reported

2. Vehicle and/or positive control

None; the test material was administered in the feed.

3. Test animals

Species: Rat
Strain: Sprague-Dawley Crl:CD^r BR
Age/weight at study initiation: males: 4 weeks, 190.9 - 246.0 g; females: 4 weeks, 149.2 - 190.5 g.
Source: Novartis Pharma AG, Basel, Switzerland.
Housing: Individually in Macrolon type 3 cages.
Diet: Certified standard diet
Water: Tap, *ad libitum*
Environmental conditions:
Temperature: 22 ± 2°C
Humidity: 55 ± 10%
Air changes: 16 - 20 air changes/hour
Photoperiod: 12 hours light/day
Acclimation period: 18 days

B. STUDY DESIGN

1. In life dates

Start: 02/02/98 End: 05/06/98

2 Animal assignment

Animals were assigned to one of 4 groups based on body weight using a computer randomization program (Table 1). Ten rats/sex/dose were given CGA-24705 at target

concentrations of 30, 300 or 3000 ppm in the diet for 3 months. Twenty rats/sex were used as controls and given 0 ppm test substance.

TABLE 1. Study design		
Target dose (ppm)	Number of animals	Actual mean dose level (mg/kg/day)
MALES		
0	20	0
30	10	2.00
300	10	20.2
3000	10	210
FEMALES		
0	20	0
30	10	2.32
300	10	23.4
3000	10	259

Data taken from pp. 21 and Section 8.2., pp. 61; MRID 44775401.

3. Dose selection rationale

Doses were selected by the sponsor based on the results of a previously conducted 2-year chronic oral toxicity study with metolachlor. The 30 and 300 ppm doses were selected as the possible NOAEL, and the 3000 ppm dose was chosen as a possible maximum tolerated dose.

4. Test diet preparation and analysis

CGA-24705 was dissolved in acetone (85 g/500 mL), and a premix was prepared using aliquots of this solution added to fixed amounts of diet. Acetone was added as needed to appropriate premixes to equalize the amount of acetone in each group's diet. After removal of acetone via evaporation, the premixes were combined with additional diet to yield appropriate concentrations of test substance for each group. Homogeneity was analyzed from samples of each diet used in weeks 1- 4 taken during the beginning, middle and end of the pelleting process. Samples of diets used in weeks 1- 4 were stored 7 weeks at room temperature for stability analysis. Concentration analysis was determined from diets used during weeks 1 - 4 and 9 - 12.

Results –

Homogeneity: Test diets were found to be homogeneous at 99 -103%.

Stability: Analysis of 30, 300 and 3000 ppm CGA-24705 in feed showed the test substance to be stable after 7 weeks at room temperature (106%, 102% and 104%, respectively).

Concentration: Concentrations of diets used during weeks 1 - 4 and 9 - 14 ranged from 98.8 - 103% of nominal.

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 and water consumption, hematology, blood chemistry, urinalysis and organ weight data were analyzed using univariate statistical analyses at each time point. Nonparametric methods were applied to allow for normal and non-normal data distributions. Each treated group was compared to control using either Lepage's or Wilcoxon's two-sample test and tested for increasing or decreasing trend from control by Jonckheere's test for ordered alternatives.

C. METHODS

1. Observations

Animals were observed twice daily for mortality and moribundity.

2. Body weight

Animals were weighed weekly throughout the study.

3. Food consumption, compound intake and water intake

Food consumption was recorded weekly. Food consumption ratios were calculated using the following formula:

$$\frac{\text{Weekly food consumption (g)}}{\text{Midweek body weight (g)}} \times \frac{1000}{7}$$

Test substance intake was calculated using the following formula:

$$\frac{\text{Food consumption ratio} \times \text{nominal dose (ppm)}}{1000}$$

Water consumption was recorded weekly based on the weight of the offered water at the beginning of a weighing period and its difference to the re-weighed amount.

4. Blood was collected from all animals at week 14 from the orbital plexus under isoflurane anesthesia for hematology and clinical biochemical analysis. All animals were fasted prior to blood collection. The CHECKED (X) parameters were examined.

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*	x	Reticulocyte count
	Blood clotting measurements*	x	Red cell volume distribution width (RDW)
x	(Thromboplastin time)	x	Hemoglobin concentration distribution width (HDW)
	(Clotting time)		
x	(Prothrombin time)		
x	(Fibrinogen)		
x	(Methemoglobin)		

* 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 electrophoresis
	Creatine phosphokinase (CPK)	x	A/G ratio
	Lactic acid dehydrogenase (LDH)		
x	Serum alanine aminotransferase (ALT)*		
x	Serum aspartate aminotransferase (AST)*		
x	Gamma glutamyl transferase (GGT)		
	Glutamate dehydrogenase (GDH)		

* Required for subchronic studies based on Subdivision F Guidelines

5. Urinalysis

Animals were placed in metabolism cages and urine was allowed to collect overnight. The CHECKED parameters were examined.

	URINALYSIS PHYSICAL/CHEMICAL EXAMINATIONS
x	Volume*
x	Specific gravity*
x	Appearance*
	Sediment*
x	pH*
x	Protein*
x	Glucose*
x	Ketones*
x	Urobilinogen
x	Bilirubin*
	Nitrites
x	Blood*
x	Leukocytes

*Required for subchronic studies based on Subdivision F Guidelines

D. OPHTHALMOLOGIC EXAMINATION

Control and high-dose males and females were examined ophthalmologically at the beginning (day -4) and end (day 86) of the study. Mydriasis was induced using Mydriaticum and the cornea, sclera, anterior chamber, lens, vitreous body and fundus were examined via indirect ophthalmoscopy. When additional examination was deemed necessary, direct and/or slit lamp ophthalmoscopy was utilized.

E. NEUROTOXICITY SCREENING

Neurotoxicity screening was not performed.

F. SACRIFICE AND PATHOLOGY

Animals were sacrificed at the end of the study via exsanguination after carbon dioxide anesthesia. Necropsies were performed on all animals. Tissues were preserved in neutral buffered 4% formalin. Paraffin embedded tissues were sectioned and stained with hematoxylin and eosin. The CHECKED (X) tissues were collected for histological examination. The (XX) organs, in addition, were weighed.

X	DIGESTIVE SYSTEM	X	CARDIOVASC./HEMAT.	X	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.)
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	Gall bladder*	xx	Epididymides	x	Thyroids*
x	Pancreas*	x	Prostate	x	Harderian gland
		x	Seminal vesicle	x	Zymbel's glands
	RESPIRATORY	xx	Ovaries		
x	Trachea*	x	Uterus*		OTHER
x	Lung*	x	vagina	x	Bone
x	Nose			x	Skeletal muscle
	Pharynx			x	Skin
	Larynx			x	All gross lesions and masses*

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

II. RESULTS

A. OBSERVATIONS

1. Toxicity No treatment-related clinical signs were observed.

2. Mortality No treatment-related deaths were reported. One 300 ppm male and one 3000 ppm female died accidentally during the study. The female died after blood collection on day 92, the circumstances surrounding the death of the male were not revealed.

B. BODY WEIGHT AND WEIGHT GAIN

No statistically significant changes in body weight or body weight gains were observed in males given CGA-24705. In females, decreased body weights were observed in animals given 300 ppm and 3000 ppm CGA-24705, however statistical significance ($p \leq 0.01$) was achieved only in 3000 ppm females at week 11. When allowing for statistical significance at the $p \leq 0.05$ level (study authors flagged data only at $p \leq 0.01$ level), body weight was statistically decreased in 300 ppm females on weeks 4 and 11 (-7% and -9%, respectively) and in 3000 ppm females from weeks 2 - 13 (-7% to -11%). Decreases in body weight in the 300 ppm group were not considered toxicologically significant due to the small magnitude of the effect.

Statistically significant decreased (22%) overall body weight gains were observed in 3000 ppm females. Thirty and 300 ppm females showed decreased total body weight

gains (-13% and -12%, respectively) without achieving statistical significance (Table 2). Only the decreased body weight gain in the 3000 ppm females is considered toxicologically significant as there was no dose-related effect at 30 and 300 ppm.

C. FOOD CONSUMPTION, COMPOUND INTAKE AND WATER CONSUMPTION

1. Food consumption

Overall food consumption data for female animals is summarized in Table 3. Statistically decreased food consumption was reported in 30, 300 and 3000 ppm females during Week 1 and in the 30 and 300 ppm group throughout the study. Overall mean food consumption was statistically decreased in 30, 300 and 3000 ppm females (-11%, -11% and -12%). No statistically significant changes in food consumption were observed in males during the study. The toxicological effect of treatment on food consumption in females is questionable as there was no dose-responsive effect and food efficiency was not affected.

(Note: One 3000 ppm female exhibited excess food spillage during the study. When data from this animal was included, mean ± SD overall food consumption was 1840.4 ± 617.3. The authors provided data that excluded food consumption from this animal, which is used in Table 2.)

2. Compound consumption

Compound consumption is shown in Table 1. Both males and females consumed comparable amounts of test substance during the study.

3. Food efficiency

Food efficiency was not significantly different for any treated group versus control during the study.

4. Water Consumption

Water consumption was statistically decreased in 300 ppm females during weeks 1, 2, 4, 6, 8 and 13 of the study. However, water consumption was statistically decreased in this group the week before being given the test material. Consequently, these changes are without toxicologic significance.

TABLE 2. Mean ± SD selected body weights (g) and total body weight gain (g) in rats administered CGA-24705 for 13 weeks.

Study Week	Treatment group (ppm)							
	Males				Females			
	0	30	300	3000	0	30	300	3000
1	265.8 ± 16.12	276.4 ± 22.65	266.3 ± 21.42	260.3 ± 24.28	190.9 ± 14.99	184.7 ± 9.79	180.7 ± 10.97	181.5 ± 8.97
4	358.3 ± 32.43	378.7 ± 40.96	355.8 ± 30.79	349.8 ± 39.18	243.3 ± 19.42	228.3 ± 14.03	226.2 ± 14.16* (-7)	225.0 ± 12.12* (-8)
9	454.8 ± 46.22	488.7 ± 64.55	455.6 ± 51.95	447.2 ± 60.71	288.3 ± 28.27	266.2 ± 19.01	262.7 ± 21.58* (-9)	259.2 ± 18.95* (-10)
11	474.5 ± 50.28	509.3 ± 70.95	479.0 ± 57.26	468.6 ± 63.51	297.7 ± 30.46	274.4 ± 15.60	270.1 ± 20.61* (-9)	263.2 ± 19.44** (-11)
13	495.0 ± 55.30	520.2 ± 67.66	496.6 ± 61.93	486.6 ± 70.33	304.2 ± 31.63	280.5 ± 19.75	277.9 ± 23.16* (-9)	271.0 ± 22.59* (-11)
Total Body Weight Gain, weeks 1-13	**273.7 ± 52.76**	**296.5 ± 54.92**	**276.6 ± 59.73**	**266.1 ± 61.00**	**135.0 ± 26.65**	**117.4 ± 15.53 (-13)**	**118.2 ± 20.17 (-12)**	**104.8 ± 16.92** (-22)**

Data taken from Tables 8.7 and 8.9, pp. 69 - 76 and 79 - 86; MRID 44775401.
Numbers in parentheses are percent difference from control calculated by reviewer
* Statistically different than control, $p \leq 0.05$.
** Statistically different versus control, $p \leq 0.01$.

TABLE 3. Selected mean ± SD weekly food consumption (g/animal/week) in female rats fed CGA - 24705 for 13 weeks.

Study Week	Treatment Group (ppm)			
	0	30	300	3000
1	132.1 ± 15.75	115.7 ± 11.11* (-12)	113.2 ± 9.10** (-14)	116.6 ± 23.55** (-12)
4	151.4 ± 18.89	133.7 ± 12.65* (-12)	132.8 ± 13.88* (-12)	159.4 ± 68.20
6	155.9 ± 19.41	136.4 ± 10.56* (-13)	137.6 ± 14.04* (-12)	154.1 ± 57.32
9	130.3 ± 18.58	119.6 ± 10.04	120.4 ± 14.39	127.7 ± 60.00
12	131.7 ± 16.19	117.9 ± 9.22* (-10)	118.0 ± 11.81	124.2 ± 19.48
Total Food Consumption, weeks 1-13	**1876.5 ± 234.9**	**1677.1 ± 134.1** (-11)**	**1669.1 ± 166.2** (-11)**	**1658.0 ± 201.8** (-12)[a]**

Data taken from Table 8.11, pp. 93 - 96, MRID 44775401.
Numbers in parentheses are percent difference from control calculated by reviewer
Overall food consumption ± SD and statistical analysis (t-test and ANOVA) calculated by the reviewer.
* Statistically different than control, $p \leq 0.05$.
** Statistically different versus control, $p \leq 0.01$.
[a] Data point excludes food consumption from one animal that exhibited excessive food spillage.

D. BLOOD WORK

1. Hematology

Changes in a number of hematologic parameters were observed in female animals during the study (Table 4); however, their toxicological significance is questionable due to the lack of a dose-response and the small magnitude of the effect. WBC were increased in 30, 300 and 3000 ppm female animals (+23%, +28% and +18%, respectively), with statistical significance achieved for only the 300 ppm group. Relative neutrophil counts were statistically decreased in 30 and 300 ppm females (-23% and -25%, respectively) and dispersion of neutrophils was statistically increased in 3000 ppm females (+25%). Relative eosinophil counts were statistically decreased in 30 and 300 ppm females (-39% and -30%, respectively) and decreased without achieving significance in 3000 ppm females (-22%). Lymphocyte counts were increased in 30, 300 and 3000 ppm animals (+29%, +37% and +19%, respectively) with statistical significance achieved in 300 ppm animals only.

TABLE 4. Selected mean ± SD hematology parameters in female rats fed CGA - 24705 for 13 weeks.				
Parameter	Treatment Group (ppm)			
	0	30	300	3000
WBC (g/L)	5.818 ± 1.889	7.128 ± 1.737 (+23)	7.471 ± 1.750** (+28)	6.865 ± 2.967 (+18)
Neutrophils (L)	0.150 ± 0.042	0.115 ± 0.025* (-23)	0.113 ± 0.063** (-25)	0.145 ± 0.084
Neutrophils (g/L)	0.873 ± 0.400	0.813 ± 0.254	0.816 ± 0.415	1.088 ± 1.011** (+25)
Eosinophils (L)	0.023 ± 0.009	0.014 ± 0.003** (-39)	0.016 ± 0.007** (-30)	0.018 ± 0.005 (-22)
Lymphocytes (g/L)	4.485 ± 1.443	5.786 ± 1.407 (+29)	6.132 ± 1.594** (+37)	5.331 ± 2.153 (+19)

Data taken from Tables 8.17, pp. 125 - 131; MRID 44775401.
* Statistically significant versus control, $p \leq 0.05$.
** Statistically significant versus control, $p \leq 0.01$.
Numbers in parentheses are percent difference from control calculated by reviewer

2. Clinical chemistry

Selected clinical chemistry parameters are summarized in Table 5. AST was statistically decreased in 3000 ppm males (-18%) and decreased without statistical significance in 3000 ppm females (-21%). Potassium was statistically increased in 3000 ppm females (+14%). Statistically increased total bilirubin was observed in 30 and 300 ppm females (+30% and +19%, respectively). Changes found in 30 ppm females only included statistically decreased glucose and creatinine (-17% and -18% respectively) and increased calcium (+3%). None of these changes is considered toxicologically significant as there was either no dose-response, the magnitude of the effect was small or the effect was contrary to that expected (AST decreased).

TABLE 5. Selected mean ± SD clinical chemistry parameters in rats fed CGA-24705 for 13 weeks.				
Parameter	Treatment Group (ppm)			
	0	30	300	3000
MALES				
AST (U/L)	77.11 ± 9.244	78.82 ± 10.53	80.73 ± 19.22	63.41 ± 6.424* (-18)
FEMALES				
AST (U/L)	76.44 ± 20.29	74.76 ± 33.45	74.46 ± 16.57	60.76 ± 13.37 (-21)
T. Bilirubin (umol/L)	2.153 ± 0.472	2.791 ± 0.348* (+30)	2.568 ± 0.522* (+19)	1.855 ± 0.407
Potassium (mmol/L)	3.332 ± 0.290	3.493 ± 0.381	3.598 ± 0.415	3.797 ± 0.347* (+14)

Data taken from Table 8.19, pp. 138 - 151; MRID 44775401.
* Statistically significant versus control, $p \leq 0.01$.
Numbers in parentheses are percent difference from control calculated by reviewer

4. URINALYSIS

Increased leukocyte counts in 3000 ppm males (+68%) were statistically significant at the $p \leq 0.05$ level (Table 6). There were no other accompanying changes, such increased pH and/or increased protein, to indicate a possible urinary tract infection. Therefore, this effect is considered coincidental.

TABLE 6. Mean ± SD urine leukocyte counts in male rats fed CGA - 24705 for 13 weeks.

Parameter	Treatment Group (ppm)			
	0	30	300	3000
Leukocytes (/ uL)	102.5 ± 140.7	111.1 ± 150.6	117.5 ± 139.0	172.5 ± 174.2* (+68)

Data taken from Table 8.21, pp. 158; MRID 44775401.
* Statistically significant versus control, $p \leq 0.05$.
Numbers in parentheses are percent difference from control calculated by reviewer

F. OPHTHALMIC EXAMINATION

No treatment-related findings were reported.

G. SACRIFICE AND PATHOLOGY

1. Organ weight

Data are summarized in Table 7. Statistically significant changes in absolute and relative organ weights were limited to decreased liver weight in 30 and 300 ppm females (-11 % and -12%, respectively), increased liver/body weight in 3000 ppm females (+9), and increased kidney/body weight in 30, 300 and 3000 ppm females (+9%, +11% and +13%, respectively). These effects are not considered toxicologically significant due to the small magnitude and the lack of accompanying histopathology changes. No statistically significant differences were observed in males.

TABLE 7. Selected mean ± SD absolute and relative organ weights in female rats fed CGA-24705 for 13 weeks.

Organ weight	Treatment Group (ppm)			
	0	30	300	3000
Liver (g)	11.00 ± 1.316	9.737 ± 0.827* (-11)	9.631 ± 0.895* (-12)	10.48 ± 1.027
% body	3.832 ± 0.303	3.679 ± 0.175	3.721 ± 0.325	4.165 ± 0.235 ** (+9)
Kidney (g)	2.021 ± 0.230	2.027 ± 0.227	2.021 ± 0.129	2.004 ± 0.206
% body	0.704 ± 0.043	0.765 ± 0.062* (+9)	0.781 ± 0.038** (+11)	0.798 ± 0.070** (+13)

Data taken from Tables 8.23 and 8.23.2, pp. 166 - 177; MRID 44775401.
* Statistically significant versus control, $p \leq 0.05$; ** Statistically significant versus control, $p \leq 0.01$.
Number in parentheses is percent difference from control calculated by reviewer
Note: % body weights presented in the study text were incorrectly calculated and were off by a factor of ten.

2. Gross pathology

No treatment-related findings were reported.

3. Microscopic pathology

No treatment-related findings were reported.

III. DISCUSSION

A. Study Author's Conclusions

The study author concluded that the NOAEL for males and females was 300 ppm, and therefore the LOAEL was 3000 ppm based on decreased body weight gain, decreased dietary intake and increased liver weight in 3000 ppm females, leukocyturia and higher plasma total protein and globulin levels in 3000 ppm males.

B. Reviewer's Conclusions

Dietary administration of 0, 30, 300 or 3000 ppm CGA-24705 to male and female rats for 13 weeks resulted in multiple effects in females at all dose levels; however, the toxicological significance of the changes at the two lower doses is questionable. No adverse effects were observed in males.

No treatment-related deaths or clinical signs occurred during the study, and there were no statistically significant changes in food efficiency, water consumption or ophthalmologic parameters. No treatment-related changes in histology parameters were reported for any treated group.

In females, decreased body weights were observed in animals given 300 ppm and 3000 ppm CGA-24705, however statistical significance ($p \leq 0.01$) was achieved only in 3000 ppm females at week 11. When allowing for statistical significance at the $p \leq 0.05$ level (study authors flagged data only at $p \leq 0.01$ level), body weight was statistically decreased in 300 ppm females on weeks 4 and 11 (-7% and -9%, respectively) and in 3000 ppm females from weeks 2 - 13 (-7% to -11%). Decreases in body weight in the 300 ppm group were not considered toxicologically significant due to the small magnitude of the effect.

Statistically significant decreased (22%) overall body weight gains were observed in 3000 ppm females. Thirty and 300 ppm females showed decreased total body weight gains (-13% and -12%, respectively) without achieving statistical significance. Only the decreased body weight gain in the 3000 ppm females is considered toxicologically significant as there was no dose-related effect at 30 and 300 ppm.

Statistically decreased food consumption was reported in 30, 300 and 3000 ppm females during Week 1 and in the 30 and 300 ppm group throughout the study. Overall mean

food consumption was statistically decreased in 30, 300 and 3000 ppm females (-11%, -11% and -12%). No statistically significant changes in food consumption were observed in males during the study. The toxicological effect of treatment on food consumption in females is questionable as there was no dose-responsive effect and food efficiency was not affected.

Changes in a number of hematologic parameters were observed in female animals during the study; however, the toxicological significance is questionable due to the lack of a dose-response and the small magnitude of the effect. WBC were increased in 30, 300 and 3000 ppm female animals (+23%, +28% and +18%, respectively), with statistical significance achieved for only the 300 ppm group. Relative neutrophil counts were statistically decreased in 30 and 300 ppm females (-23% and -25%, respectively) and dispersion of neutrophils was statistically increased in 3000 ppm females (+25%). Relative eosinophil counts were statistically decreased in 30 and 300 ppm females (-39% and -30%, respectively) and decreased without achieving significance in 3000 ppm females (-22%). Lymphocyte counts were increased in 30, 300 and 3000 ppm animals (+29%, +37% and +19%, respectively) with statistical significance achieved in 300 ppm animals only.

AST was statistically decreased in 3000 ppm males (-18%) and decreased without statistical significance in 3000 ppm females (-21%). Potassium was statistically increased in 3000 ppm females (+14%). Statistically increased total bilirubin was observed in 30 and 300 ppm females (+30% and +19%, respectively). Changes found in 30 ppm females only included statistically decreased glucose and creatinine (-17% and -18% respectively) and increased calcium (+3%). None of these changes is considered toxicologically significant as there was either no dose-response, the magnitude of the effect was small or the effect was contrary to that expected (AST decreased).

Statistically significant changes in absolute and relative organ weights were limited to decreased liver weight in 30 and 300 ppm females (-11 % and -12%, respectively), increased liver/body weight in 3000 ppm females (+9), and increased kidney/body weight in 30, 300 and 3000 ppm females (+9%, +11% and +13%, respectively). These effects are not considered toxicologically significant due to the small magnitude and the lack of accompanying histopathology changes. No statistically significant differences were observed in males.

The LOAEL for female Sprague-Dawley rats was 3000 ppm (259 mg/kg/day) based on decreased body weight and body weight gain. The NOAEL for females was 300 ppm (23.4 mg/kg/day). The LOAEL for male Sprague-Dawley rats was not established. The NOAEL for males was 3000 ppm (210 mg/kg/day).

B. STUDY DEFICIENCIES

Minor deficiencies were noted; none affected the validity of the study.

1. Percent body weights were calculated incorrectly in the study.

2. The study author concluded that "Oral administration of CGA-24705 . . : resulted in . . . higher plasma total protein and globulin levels for males at 3000 ppm;. . . ." Data supplied in the results section show no increase in these parameters.

3. Urine sediment data was not included.