1-8-2001

DATA EVALUATION REPORT

CGA-77102

STUDY TYPE: SUBCHRONIC ORAL TOXICITY - RAT [OPPTS 870.3100 (§82-1a)]
MRID 44775402

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 Study -Rat [OPPTS 870.3100 (§82-1a)]

DP BARCODE: D254363
P.C. CODE: 108800

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

TEST MATERIAL (PURITY): CGA-77102 tech.(a.i. 98.5%)

SYNONYMS: Metolachlor, alphametolachlor

CITATION: Fankhauser, H. (1999) CGA-77102 Final Report. 3-month oral toxicity study in rats (administration in food). Novartis Crop Protection AG, Toxicology, 4332 Stein, Switzerland. Study ID # 971144, Novartis # 1161-98. January 25, 1999. MRID 44775402. Unpublished.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 44775402), groups of male and female Sprague-Dawley rats (20/sex for controls, 10/sex/ treated group) were given CGA-77102 (a.i. 98.5 %, Lot/Batch P.501001) administered in feed at 0, 30, 300 or 3000 ppm (equivalent to 0, 1.90, 20.4 and 208.0 mg/kg/day for males and 0, 2.13, 23.9 and 236.0 mg/kg/ day for females).

No treatment-related deaths or clinical signs occurred during the study, however, one control female was sacrificed before schedule because of overall poor condition. No statistically significant changes in total body weight, body weight gain, food consumption or food efficiency were reported. There were no treatment-related changes in ophthalmologic or histopathology parameters.

Small, sporadic statistically significant changes in hematology parameters were observed during the study. These included increased MCHC in 30 ppm males (+2%), increased methemoglobin concentration (MetHb) in 3000 ppm males and females (both +13%), and decreased platelet count in 30 ppm females (-14%). Statistically significant changes in clinical chemistry parameters included decreased glucose (-14%), creatinine (-14%), chloride (-3%) and increased urea (+13%), globulin (+10%), and calcium (+5%) in 3000 ppm males, decreased bilirubin (-28%), AST (-29%), ALT (-36%) and A/G (-6%) in 3000 ppm females and AST in 300 ppm females (-24%). These changes are of no toxicological or biological concern.

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Statistically significant changes in urinalysis parameters included increased mean volume (+48%), decreased relative density (-2%) and decreased ketones (-52%) in 300 ppm males, and decreased relative density (-2%) in 30 ppm males. These changes also are of no toxicological or biological concern.

Statistically significant changes in absolute organ weight were limited to increased ovary weight in 30 ppm females (+13%). Increased relative organ weights included ovary/body in 300 ppm females (+14%), liver/ body in 3000 ppm males and females (+16% and +7%, respectively), kidney/body in 3000 ppm males (+14%), and spleen/body in 300 and 3000 ppm males (both +13%).

Under the conditions of this study, a LOAEL for male and female Sprague-Dawley rats cannot be defined. The NOAEL for male and female rats is 3000 ppm (equivalent to 208 mg/kg/day in males and 236 mg/kg/day in females).

This study is classified as **Unacceptable/Guideline [OPPTS 870.3100 (§82-1a)]** and does not satisfy the Subdivision F guideline requirements. The highest dose tested did not show a toxicological effect.

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

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: CGA-77102 tech.

   Description: Oily liquid
   Lot/Batch # : P. 501001
   Purity: a.i. 98.5%
   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: Crl:CD^r BR
   Age/weight at study initiation: males: 4 weeks, 219 - 286 g; females: 4 weeks, 154 - 227 g.
   Source: Novartis Pharma AG, Basel, Switzerland.

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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: 20 days

B. STUDY DESIGN

1. In life dates

Start: 02/04/98 End: 05/08/98

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-77102 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	1.90
300	10	20.4
3000	10	208
FEMALES		
0	20	0
30	10	2.13
300	10	23.9
3000	10	236

Data taken from pp. 39; MRID 44775402.

3. Dose selection rationale

Doses were selected by the sponsor based on the results of previously conducted short- and long-term studies so that 30 ppm would cause no observable adverse

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effects, 300 ppm would cause slight effects, and 3000 ppm would cause adverse effects with few or no fatalities.

4. Test diet preparation and analysis

CGA-77102 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 during 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 97% - 101.5% of target concentration..

Stability: Analysis of 30, 300 and 3000 ppm CGA-77102 in feed showed the test substance to be stable after 7 weeks at room temperature (98%, 101% and 103%, respectively).

Concentration: Concentrations of diets used during weeks 1 - 4 and 9 - 14 ranged from 95.9 % - 104% 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.

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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 after one day.

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

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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 at the end of the study 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 -5) and end (day 87) of the study. In addition, examinations of 300 ppm males were conducted on day 87. 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*		GLANDULAR
x	Ileum*		UROGENITAL	xx	Adrenal gland*
x	Cecum*	xx	Kidneys*+	x	Lacrimal gland[T]
x	Colon*	x	Urinary bladder*	x	Mammary gland[T]
x	Rectum*	xx	Testes*+	x	Parathyroids*
xx	Liver*+	xx	Epididymides	x	Thyroids+
x	Gall bladder*	x	Prostate	x	Harderian gland
x	Pancreas*	x	Seminal vesicle	x	Zymbel's glands
	RESPIRATORY	xx	Ovaries		OTHER
x	Trachea*	x	Uterus*	x	Bone
x	Lung*	x	vagina	x	Skeletal muscle
x	Nose			x	Skin
	Pharynx			x	All gross lesions and masses*
	Larynx				

* 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. One control female displayed ataxia, pale eyes, hunched posture, hypoactivity and piloerection during the study.

2. Mortality No treatment-related deaths were reported. The control female described above was sacrificed because of poor overall condition on day 62.

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B. BODY WEIGHT AND WEIGHT GAIN

No statistically significantly decreases in body weight or body weight gains were observed in any treatment group (Table 2).

TABLE 2. Selected mean ± SD body weights (g) and total body weight gain (g) in rats administered CGA-77102 for 13 weeks.

Week	Treatment group (ppm)							
	Males				Females			
	0	30	300	3000	0	30	300	3000
1	286.1 ± 25.89	280.6 ± 18.06	287.3 ± 36.23	279.8 ± 12.70	201.6 ± 15.84	206.2 ± 18.71	202.2 ± 13.09	195.2 ± 16.17
5	392.2 ± 50.22	383.3 ± 30.09	396.4 ± 54.08	374.1 ± 24.85	249.9 ± 24.79	252.5 ± 24.05	256.4 ± 21.76	238.9 ± 20.42
9	465.7 ± 63.58	452.1 ± 36.90	472.2 ± 64.18	436.5 ± 34.78	268.6 ± 42.29	275.1 ± 24.80	284.6 ± 26.54	260.2 ± 20.69
13	504.6 ± 71.10	486.3 ± 42.78	510.8 ± 72.90	467.6 ± 46.00	281.8 ± 33.02	278.9 ± 26.20	294.5 ± 29.69	267.6 ± 21.80
Total Body Wt. Gain	**255.4 ± 57.74**	**238.9 ± 33.65**	**257.7 ± 53.45**	**219.0 ± 43.44**	**98.76 ± 22.72**	**95.57 ± 18.69**	**112.9 ± 23.76**	**86.41 ± 12.17**

Data taken from Tables 8.7 and 8.8, pp. 69 - 86; MRID 44775402.

C. FOOD CONSUMPTION, COMPOUND INTAKE AND WATER CONSUMPTION

1. Food consumption

No statistically significant changes in food consumption were observed during the study.

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

Data is summarized in Table 3. Water consumption was statistically increased in 300 ppm males at weeks 2, 4, 6, 9, 11 and 12 (+12 to +22%). While weekly water consumption was not statistically different for any other treated group, weekly differences in 3000 ppm females ranged from +10% to +27% throughout the study. Overall mean water consumption was increased in 30, 300 and 3000 ppm males (+4%, +16% and

+3%, respectively) and in 30, 300 and 3000 ppm females (+2%, +7% and +18%, respectively) without achieving statistical significance.

TABLE 3. Mean water consumption (g/animal/week) ± SD in rats administered CGA-77102 for 13 weeks.

Week	Treatment group (ppm)							
	Males				Females			
	0	30	300	3000	0	30	300	3000
1	196.0 ± 32.05	208.5 ± 21.87	219.0 ± 41.24	197.1 ± 23.32	161.0 ± 34.07	154.8 ± 39.34	169.8 ± 27.59	196.8 ± 56.30 (+22)[a]
2	207.3 ± 44.18	221.6 ± 27.22	232.8 ± 35.63* (+12)	213.6 ± 31.95	174.3 ± 33.25	180.7 ± 30.47	184.6 ± 22.23	209.9 ± 43.56 (+20)
3	204.1 ± 39.05	213.6 ± 28.64	230.2 ± 40.29	206.4 ± 42.38	163.1 ± 40.52	178.5 ± 35.05	171.9 ± 17.37	179.8 ± 48.63 (+10)
4	213.5 ± 39.81	233.3 ± 34.94	251.4 ± 42.22* (+18)	218.0 ± 44.58	166.8 ± 34.24	164.5 ± 33.78	180.2 ± 34.58	201.8 ± 60.01 (+21)
5	216.0 ± 44.09	219.0 ± 31.95	246.2 ± 40.27	210.7 ± 49.22	167.0 ± 28.24	173.3 ± 48.49	174.2 ± 38.97	189.8 ± 60.49 (+14)
6	217.5 ± 38.91	239.3 ± 36.40	264.8 ± 43.92* (+22)	226.7 ± 49.06	190.6 ± 34.95	191.9 ± 64.71	205.7 ± 25.15	217.4 ± 56.57 (+14)
7	224.2 ± 51.63	219.3 ± 30.11	253.1 ± 42.62	221.6 ± 52.13	165.4 ± 41.72	173.0 ± 34.16	176.1 ± 15.83	197.2 ± 63.80 (+19)
8	213.7 ± 33.50	223.1 ± 26.64	254.2 ± 52.54	217.9 ± 57.84	156.1 ± 40.67	172.9 ± 36.67	168.2 ± 32.15	186.7 ± 54.32 (+20)
9	210.3 ± 39.21	210.8 ± 22.56	250.2 ± 41.65* (+19)	228.6 ± 58.55	171.3 ± 51.28	179.7 ± 61.39	183.7 ± 22.23	200.8 ± 48.92 (+17)
10	189.3 ± 35.37	187.0 ± 21.20	210.8 ± 47.41	202.0 ± 36.28	144.8 ± 36.49	136.1 ± 40.05	156.5 ± 18.16	168.1 ± 47.31 (+16)
11	212.1 ± 42.58	211.3 ± 18.93	251.5 ± 33.16* (+19)	213.4 ± 49.51	165.6 ± 37.92	165.3 ± 40.19	176.1 ± 13.59	190.1 ± 63.03 (+15)
12	198.8 ± 39.34	225.4 ± 42.47	235.8 ± 42.45* (+19)	215.0 ± 53.25	163.9 ± 30.05	168.1 ± 36.28	165.1 ± 26.52	197.3 ± 70.18 (+20)
13	207.7 ± 52.66	218.6 ± 37.64	240.2 ± 41.73	224.3 ± 58.86	162.4 ± 30.81	164.4 ± 42.49	181.9 ± 35.42	206.7 ± 56.31 (+27)
Overall	**2710.5 ± 531.6**	**2830.8 ± 380.6 (+4)**	**3140.2 ± 545.1 (+16)**	**2795.3 ± 606.9 (+3)**	**2152.3 ± 474.2**	**2203.2 ± 473.3 (+2)**	**2294.0 ± 329.8 (+7)**	**2542.4 ± 729.4 (+18)**

Data taken from Table 8.15 pp. 102 - 109 and pp 42; MRID 44775402.

[a] Percent difference from control calculated by reviewer

* Statistically significant versus control, $p \leq 0.01$.

Data for overall water consumption is sum of weekly group means ± sum of weekly group SD.

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D. BLOOD WORK

1. Hematology

Small, sporadic statistically significant changes in hematology parameters were observed during the study (Table 4). These included increased MCHC in 30 ppm males (+2%), increased methemoglobin concentration (MetHb) in 3000 ppm males and females (both +13%), and decreased platelet count in 30 ppm females (-14%).

TABLE 4. Selected mean ± SD hematology parameters in rats fed CGA-77102 for 13 weeks.

Parameter	Treatment Group (ppm)			
	0	30	300	3000
MALES				
MCHC (mmol/L)	19.83 ± 0.341	20.23 ± 0.310* (+2)[a]	19.90 ± 0.298	20.04 ± 0.201
MetHb (L)	0.008 ± 0.001	0.008 ± 0.001	0.008 ± 0.001	0.009 ± 0.001* (+13)
FEMALES				
MetHb (L)	0.008 ± 0.001	0.008 ± 0.001	0.009 ± 0.001	0.009 ± 0.001* (+13)
Platelets (G/L)	1059 ± 106.1	911.3 ± 160.7* (-14)	1016 ± 93.39	950.1 ± 159.0

Data taken from Tables 8.17, pp. 116 - 133; MRID 44775402.
* Statistically significant versus control, $p \leq 0.01$.
[a] Percent difference from control calculated by reviewer

2. Clinical chemistry

Clinical chemistry parameters are summarized in Table 5. In 3000 ppm males, statistically significant changes in glucose (-14%), creatinine (-14%), globulin (+10%), calcium (+5%), chloride (-3%), and urea (+13%) were observed during the study. Statistically significant decreases in bilirubin (-28%), AST (-29%), ALT (-36%) and A/G (-6%) were found in 3000 ppm females and AST in 300 ppm females (-24%).

TABLE 5. Selected mean ± SD clinical chemistry parameters in rats fed CGA-77102 for 13 weeks.				
Parameter	Treatment Group (ppm)			
	0	30	300	3000
MALES				
Glucose (mmol/L)	7.399 ± 0.786	7.127 ± 0.831	6.747 ± 0.537	6.327 ± 0.823*(-14)[a]
Creatinine (umol/L)	21.44 ± 2.170	22.55 ± 1.795	21.23 ± 2.131	18.47 ± 4.324*(-14)
Globulin (g/L)	36.91 ± 2.900	37.39 ± 1.643	37.47 ± 2.413	40.48 ± 2.635*(+10)
Calcium (mmol/L)	2.713 ± 0.078	2.749 ± 0.050	2.713 ± 0.072	2.848 ± 0.118*(+5)
Chloride (mmol/L)	101.9 ± 2.050	99.07 ± 1.570	100.5 ± 1.022	98.39 ± 2.153*(-3)
Urea (umol/L)	4.921 ± 0.421	5.076 ± 0.479	5.280 ± 0.803	5.543 ± .1101*(13)
FEMALES				
Bilirubin (umol/L)	2.373 ± 0.328	2.786 ± 0.680	2.276 ± 0.380	1.698 ± 0.320*(-28)
AST (U/L)	84.76 ± 27.38	106.8 ± 106.6	64.01 ± 6.359# (-24)	60.59 ± 10.70*(-29)
ALT (U/L)	37.04 ± 19.66	46.77 ± 53.38	24.86 ± 4.142	23.86 ± 4.897*(-36)
A/G (L)	1.117 ± 0.063	1.143 ± 0.107	1.088 ± 0.063	1.049 ± 0.035*(-6)

Data taken from Table 8.19, pp. 138 - 151; MRID 44775402.
*Statistically significant versus control, $p \leq 0.01$.
Statistically significant versus control, $p \leq 0.05$.
[a] Percent difference from control.

4. URINALYSIS

Statistically significant changes in urinalysis parameters included increased mean volume (+48%), decreased relative density (-2%) and decreased ketones (-52%) in 300 ppm males, and decreased relative density (-2%) in 30 ppm males. Increased leukocytes (+157%) in 3000 ppm males did not achieve statistical significance (Table 6).

TABLE 6. Selected mean ± SD urinalysis parameters in male rats fed CGA-77102 for 13 weeks.				
Parameter	Treatment Group (ppm)			
	0	30	300	3000
Volume (mL)	4.680 ± 1.383	6.110 ± 1.447	6.930 ± 1.686* (+48)[a]	3.860 ± 1.332
Relative density (L)	1.067 ± 0.013	1.049 ± 0.013* (-2)	1.050 ± 0.021* (-2)	1.064 ± 0.014
Ketones (mmol/L)	1.150 ± 0.489	0.850 ± 0.580	0.550 ± 0.550* (-52)	1.100 ± 0.516
Leukocytes (per/uL)	82.50 ± 105.2	55.00 ± 38.73	77.50 ± 36.23	212.3 ± 199.7 (+157)

Data taken from Table 8.21, pp. 156 - 161; MRID 44775402.
* Statistically significant versus control, $p \leq 0.01$.
[a] Percent difference from control calculated by reviewer

F. OPHTHALMIC EXAMINATION

No treatment-related findings were reported.

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G. SACRIFICE AND PATHOLOGY

1. Organ weight

Selected absolute and relative organ weight data are summarized in Table 7. Changes in absolute organ weight were limited to increased ovary weight in 30 ppm (+13%) and 300 ppm females (+15%), however statistical significance was achieved only in the 300 ppm group. Ovary to body weight ratios were statistically increased in 300 ppm females only (+14%). Liver/ body weight was statistically increased in 3000 ppm males and females (+16% and +7%, respectively), kidney/body weight ratio was increased in 3000 ppm males (+14%), and spleen/body weight ratio was increased in 300 and 3000 ppm males (both +13%).

TABLE 7. Selected mean ± SD absolute and relative organ weights in rats fed CGA-77102 for 13 weeks.

Organ weight	Treatment Group (ppm)			
	0	30	300	3000
MALES				
Liver (g) % body	18.68 ± 2.762 3.894 ± 0.3612	17.21 ± 2.245 3.708 ± 0.2471	19.10 ± 3.002 3.937 ± 0.2944	20.29 ± 2.760 4.524 ± 0.3224* (+16)[a]
Kidney (g) % body	3.265 ± 0.481 0.6803 ± 0.0533	2.942 ± 0.350 0.6356 ± 0.0551	3.347 ± 0.452 0.6908 ± 0.0351	3.490 ± 0.430 0.7807 ± 0.0719* (+14)
Spleen (g) % body	0.756 ± 0.111 0.1577 ± 0.0150	0.784 ± 0.123 0.1695 ± 0.0251	0.853 ± 0.075 0.1775 ± 0.0179# (+13)	0.781 ± 0.100 0.1755 ± 0.0249* (+13)
FEMALES				
Liver (g) % body	10.26 ± 1.280 3.804 ± 0.1667	9.945 ± 0.879 3.756 ± 0.1845	9.954 ± 1.218 3.634 ± 0.1661	10.30 ± 0.879 4.089 ± 0.2865*(+7)
Ovary (mg) % body	171.3 ± 17.12 0.0639 ± 0.0068	193.6 ± 26.15 0.0736 ± 0.0122	197.7 ± 29.16* (+15) 0.0729 ± 0.0121*(+14)	178.1 ± 32.96 0.0707 ± 0.0131

Data taken from Tables 8.23 and 8.23.2, pp. 166 - 177; MRID 44775402.
* Statistically significant versus control, $p \leq 0.01$.
# Statistically significant versus control, $p \leq 0.05$.
[a] 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.

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III. DISCUSSION

A. DISCUSSION

Dietary administration of 0, 30, 300 or 3000 ppm CGA-77102 to male and female rats for 13 weeks resulted in very slight alterations in a few parameters without establishing clear toxicologic significance for any changes observed.

No treatment-related deaths, clinical signs, statistically significant changes in total body weight, body weight gain, food consumption or food efficiency were reported. There were no treatment-related changes in ophthalmologic or histopathologic parameters.

Overall mean water consumption was increased in 30, 300 and 3000 ppm males (+4%, +16% and +3%, respectively) and in 30, 300 and 3000 ppm females (+2%, +7% and +18%, respectively) without achieving statistical significance. While a trend for increased water consumption may be inferred and the increases may have affected some other parameters, the toxicologic relevance for these small increases is minimal.

The changes in clinical chemistry parameters that achieved statistical significance were not indicative of a pattern of toxicologic effects. Decreased glucose (-14%), creatinine (-14%), chloride (-3%) and increased urea (+13%), globulin (+10%) and calcium (+5%) in 3000 ppm males, decreased bilirubin (-28%), AST (-29%), ALT (-36%) and A/G (-6%) in 3000 ppm females and AST in 300 ppm females (-24%) may be related to the increased water intake, but do not suggest adverse affects. Likewise, statistically significant changes in hematologic parameters – increased MCHC in 30 ppm males (+2%), increased methemoglobin concentration (MetHb) in 3000 ppm males and females (both +13%), and decreased platelet count in 30 ppm females (-14%) – were small and sporadic and had no apparent toxicologic or biologic significance.

Statistically significant changes in urinalysis parameters [increased mean volume (+48%), decreased relative density (-2%) and decreased ketones (-52%) in 300 ppm males, and decreased relative density (-2%) in 30 ppm males] also may be related to increased water intake but showed no dose-response and are not likely to adversely effect the animals. The increased leukocyte counts in 3000 ppm males (+157%), were attributed to increased counts in several animals and similar increases were found in control rats. Therefore, the increases are not of toxicologic or biologic concern. The statistically significant increases in organ weights [ovary weight in 30 ppm females (+13%), ovary/body weight in 300 ppm females (+14%), liver/ body weight in 3000 ppm males and females (+16% and +7%, respectively), kidney/body weight in 3000 ppm males (+14%), and spleen/body weight in 300 and 3000 ppm males (both +13%)] may be indicative of organ hypertrophy, but cannot be confidently designated as toxic effects without concomitant histopathology.

While the study author concludes that 3000 ppm doses caused toxic effects (decreased body weight development, leukocyturia, higher plasma total protein and globulin levels associated with lower A/G, and increased relative liver weight in 3000 ppm males; increased water consumption and relative liver weight in 3000 ppm females) and should

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constitute the LOAEL, it is the reviewers opinion that the results of this study do not substantiate this conclusion. The highest doses given, 3000 ppm for both males and females, failed to show a clear pattern of adverse toxic effects. Therefore, based on the results of this study, a LOAEL cannot be determined.

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. Urine sediment data was not included.

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