(9-29-97)

EPA Reviewer: Linda L. Taylor, Ph.D.
Review Section II, Toxicology Branch II (7509C)
Branch Senior Scientist: Whang Phang, Ph.D.
Reregistration Branch I, Health Effects Division (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Combined Chronic Toxicity/Carcinogenicity [feeding]-rat OPPTS 870.4300 [§83-5]

DP BARCODE: D232217
P.C. CODE: 128959
REREGISTRATION CASE #: 060640

SUBMISSION CODE: S515138
TOX. CHEM. NO.: 463 O

TEST MATERIAL (PURITY): Fluroxypyr [99.0%]

SYNONYMS: 4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy acetic acid; DOWCO*433

CITATION: Quast, J.F. and McGuirk, R.J. (1995) Fluroxypyr: Two-Year Dietary Chronic Toxicity/Oncogenicity Study in Fischer 344 Rats. The Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical Company. Laboratory Project Study ID K-129976-008, dates of experimental work [February 21, 1992 - February 24, 1994]. MRID 44080322. Unpublished.

SPONSOR: DowElanco

EXECUTIVE SUMMARY: In the combined chronic toxicity/carcinogenicity study in rats [MRID 44080322], Fluroxypyr [99.0% a.i.] was administered to 50 Fischer 344 rats/sex/dose via the diet at dose levels of 0, 100, 500, and 1000 [females only] mg/kg/day for 24 months [10 rats/sex/dose for 12 months]. At the high-dose level, there was an increase in death of both sexes, and the males at this dose level were terminated on day 118 [6 deaths prior to day 112] following erratic body-weight gains, changes in clinical chemistry findings indicative of impaired renal function, and a thin appearance. The high-dose females had a 42% mortality rate, with 48% of the deaths attributed to renal failure. Body-weight gain during the first 90-day interval was decreased [79% of control] in males at the high dose but comparable to control for females. Overall body-weight gain of the high-dose females was decreased [69% of control] compared to the control. Food consumption was not adversely affected overall. There were no consistent findings in hematology, clinical chemistry, or urinalysis parameters monitored, although the changes noted on several occasions were consistent with kidney effects and/or nutritional condition of the rat. Kidney weight was increased at the 500 mg/kg/day dose level in males and at all three dose levels in females, although the increase at the low-dose level appears to be within that of the historical control. Gross and microscopic lesions characteristic of renal toxicity [decreased size, papillary necrosis, and roughened surface] were observed in the high-dose males sacrificed on day 118. At study termination, chronic progressive glomerulonephropathy [CPG] of a severe or very severe degree was slightly increased in males at 500 mg/kg/day when compared to the low-dose and

control males and was slightly higher than the historical control. In females at study termination, increased severity of renal CPG was observed at the 500 and 1000 mg/kg/day dose levels, compared to the control and low-dose groups. Other changes observed [decreased body fat, gastric erosion/ulcers of glandular mucosa] were considered secondary changes due to the nutritional state of the rat. Histologically, hyperplasia of the pelvic epithelium, papillary necrosis, and tubular nephrosis were observed at the 500 mg/kg/day in males and at 1000 mg/kg/day in females at study termination. There was no apparent increase in the incidence of kidney tumors in either sex. With the exception of an increased incidence of parafollicular cell adenomas [single only] in males at 500 mg/kg/day, at the doses tested, there was no apparent treatment-related increase in any tumor type in either sex.

The LOEL is 500 mg/kg/day], based on increased kidney weight in both sexes, increased incidence of atrophy, adipose tissue [mesenteric tissues] in males and an increase in the severity of chronic progressive glomerulonephropathy in the kidney in both sexes. The NOEL is 100 mg/kg/day]. Deaths occurred at 1000 mg/kg/day in males within the first 90 days on test [2 by day 28 and 3 more by day 56].

This guideline [§83-5] combined chronic toxicity/carcinogenicity study in the rat is Acceptable.

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

2

I. MATERIALS AND METHODS

A. MATERIALS

1. Test Material: Fluroxypyr
Description: white solid
Lot #: AGR# 295035
Purity: 99.0% a.i.
Stability of Compound: stable over duration of study [Table 3, page 86]
CAS #: 69377-81-7
STRUCTURE

2. Vehicle: basal diet

3. Test animals
Species: rat
Strain: Fischer 344
Age at study initiation: ≈5 weeks at purchase
Weight at study initiation: ♂♂ ≈161-165 g/♀♀ ≈107 g on day -2
Source: Charles River Laboratories, Kingston, NY
Housing: 2/cage [♀♀ throughout study; ♂♂ for first 602 days, singly thereafter due to size and weight relative to cage size
Diet: Purina Certified Chow #5002 ad libitum
Water: tap water ad libitum
Environmental conditions: normal laboratory conditions
Acclimation period: 17 days

B. STUDY DESIGN

1. In life dates - start: February 21, 1992; end: February 24, 1994

2. Animal assignment - Rats [60/sex/group] were assigned [computer-generated randomization scheme based on body weight of each sex] to 1 of 4 test groups and feed diets formulated to provide doses of 0, 100, 500, or 1000 mg Fluroxypyr/kg body weight/day for 24 months. Ten of these rats/sex/group were selected randomly and predesignated at the start of the study as a satellite group to be sacrificed after ≈12 months to assess chronic toxicity. NOTE: Due to kidney toxicity, all surviving high-dose males were removed from the study on test day 118 and necropsied.

3. Dose Selection: The limit dose, 1000 mg/kg/day, was chosen as the high dose since it had not been found to cause any significant adverse effects in a subchronic [90-day] oral toxicity study in Fischer 344 rats [MRID 44080316]. The two other dose levels were chosen to assess possible dose-response relationships and a NOEL. The low-dose level was based on previous studies in the Wistar rat.

4. Diet preparation and analysis: Test diets were prepared by serial dilution of a premix [test material-feed concentrate], and the diets were prepared weekly during the first 13 weeks and at least once every

2 weeks thereafter. Premixes were mixed every 2-4 weeks throughout the study, based on the stability of the test material in the feed. Initial concentrations of the diet were based on pretest body weight and feed consumption data, and thereafter, the most recent body weight and feed consumption data for each sex/dose were used to adjust the concentration of the test material in the diets to maintain the targeted dose levels. Dietary concentrations were adjusted weekly during weeks 1-13 and at 4-week intervals thereafter. Stability of the test material in the basal diet was analyzed concurrently with the study. Homogeneity of the diets was analyzed 3 times during the study, and test diets were analyzed during weeks -2, 3, 13, 29, 38, 50, 65, 81, 93, and 101 to determine the concentration of the test material achieved. The purity of the test material was checked at ≈6-month intervals.

Results

Homogeneity Analysis: The diets were found to be mixed homogeneously [Table 5, page 88 of the report; relative standard deviation ranged from 2.61% to 4.75%] .

Stability Analysis: Fluroxypyr in the basal rodent chow was established to be at least 35 days in a previous study and ≥28 days in a study run concurrently with the current rat 2-year study [Table 4, page 87] .

Concentration Analysis: The test diets were found to contain the acceptable amounts of test material. Measured concentrations ranged from 88-102% and averaged from 93-98% of the targeted concentrations.

Test Material Analysis: Prior to study initiation, the purity of Fluroxypyr was found to be 99.0%. Analysis at various time points during the study found the purity to range from 98.7% to 99.2% [Table 3, page 86 of the report] .

5. There was no statement as to how often fresh food was provided.

6. Statistics - Feed consumption, feed efficiency, and white blood cell differential counts: Descriptive statistics only [means and standard deviations]. Body weights, organ weights, clinical chemistry, urine specific gravity, and appropriate hematology data: Bartlett's test for equality of variances; based on outcome, exploratory data analyses were performed by a parametric or nonparametric analysis of variance [ANOVA], followed respectively by Dunnett's test or the Wilcoxon Rank-Sum test with a Bonferroni correction for multiple group comparisons. Statistical outliers were identified by a sequential test [Grubbs] but routinely excluded only from food consumption statistics. Histopathologic observations: [for tissues scheduled for examination from all rats] incidences first tested for deviation from linearity using ordinal spacings of doses; if linearity not rejected, data tested for linear trend using Cochran-Armitage test; if significant or if significant deviation from linearity found, incidences for each group compared to control using a pairwise Chi-square test with Yate's

continuity correction. [for tissues scheduled for examination from all control, all high, and only selected mice from other groups] analysis limited to pairwise comparisons of control and high dose using pairwise Chi-square test with Yate's continuity correction. Mortality patterns: Gehan-Wilcoxon procedure for all scheduled terminal sacrifice rats. Since there was a significant increase in mortality in the female 1000 mg/kg/day group compared to the controls, mortality-adjusted analyses [Gart] were performed for the control versus the high-dose comparison in tumors in females.

C. METHODS

1. Observations

Rats were examined at least once a day for mortality, moribundity, availability of feed and water, and signs of toxicity. Once a week and prior to start of study, each mouse was given a detailed examination for signs of toxicity that included palpation for masses. Each rat was examined specifically for tremors, convulsions, lethargy, and other signs of effects related to central nervous system function, salivation and diarrhea.

2. Body weight

Individual body weights were recorded prior to study, once weekly for the first 13 weeks, and at least every 4 weeks thereafter.

3. Food consumption

Food consumption was calculated pre-test, weekly for the first 13 weeks, and for a one-week period every month thereafter by weighing feed crocks before and after feeding and using the formula below. Feed efficiency was calculated for the first 13 weeks [see below].

$$\text{feed consumption [g/day]} = \frac{\text{[initial wt. feeder - final wt. feeder]}}{\text{[\# days in measurement cycle] [\# rats/cage]}}$$

$$\text{feed efficiency [g feed consumed/g body-weight gain/day]} = \frac{\text{[g feed consumed/day]}}{\text{[g body weight gain/day]}}$$

4. Ophthalmoscopic examinations: Ophthalmological examinations were conducted on all rats prior to study initiation [pen light illumination] and at the scheduled 12- and 24-month necropsies [using moistened slide/fluorescent light technique]. Additionally, the eyes of all surviving rats of the chronic toxicity/carcinogenicity group were examined the week prior to the 24-month necropsy [pen light illumination].

5. Clinical Pathology

To the extent possible, the same rats that were designated for the 12-month sacrifice were used for the hematology, clinical chemistry, and urinalysis determinations at 6 and 12 months. At 18 months, the first

10 surviving rats/sex/dose were used for clinical pathology assessment. Samples for the hematology and clinical chemistry determinations for the 24-month phase of the study were collected on test day 726 [≈1 week prior to necropsy] from the first 20 surviving rats of each group, and the urinalysis samples were collected from 10 of these same rats during the week prior to necropsy. The rats were fasted overnight prior to the hematology and clinical chemistry sample collections, and the urinalysis samples were collected within the same week as the blood samples, but the rats were not fasted prior to sample collection. Blood was obtained via the orbital sinus of fasted rats anesthetized with methoxyflurane. Blood samples were treated with anticoagulant, EDTA, and blood smears were prepared and stained with Wright's stain. Blood smears were prepared for all rats from which blood samples were collected. The CHECKED (X) parameters were examined.

a. Hematology

X	Hematocrit (HCT)	X	Leukocyte differential count*
X	Hemoglobin (HGB)		Mean corpuscular HGB (MCH)
X	Leukocyte count (WBC)		Mean corpusc. HGB conc.(MCHC)
X	Erythrocyte count (RBC)		Mean corpusc. volume (MCV)
X	Platelet count		Reticulocyte count
	Blood clotting measurements	X	Morphology
	(Thromboplastin time)		
	(Clotting time)		
	(Prothrombin time)		

b. Clinical Chemistry

X	ELECTROLYTES	X	OTHER
X	Calcium	X	Albumin
X	Chloride	X	Blood creatinine
	Magnesium	X	Blood urea nitrogen
X	Phosphorus	X	Total Cholesterol
X	Potassium	X	Globulins [calculated]
X	Sodium	X	Glucose
		X	Total bilirubin
	ENZYMES	X	Total serum protein (TP)
X	Alkaline phosphatase (ALK)	X	Triglycerides
	Cholinesterase (ChE)		Serum protein electrophoresis
X	Creatine phosphokinase		
	Lactic acid dehydrogenase (LDH)		
X	Serum alanine amino-transferase		
X	Serum aspartate amino-transferase		
	Gamma glutamyl transferase (GGT)		
	Glutamate dehydrogenase		

c. Urinalysis

X		X	
X	Appearance	X	Glucose
	Volume	X	Ketones
X	Specific gravity	X	Bilirubin
X	pH	X	Blood
X	Sediment (microscopic)		Nitrate
X	Protein	X	Urobilinogen

6. Sacrifice and Pathology

All rats were subjected to a gross pathological examination, and the CHECKED (X) tissues were collected for histological examination. Rats of the scheduled sacrifice groups were fasted overnight and terminal body weights were recorded and each was anesthetized with methoxyflurane prior to decapitation and exsanguination. All external tissues and orifices were examined, and the eyes were visually examined by pressing a moistened glass microscopic slide to each cornea under a florescent light. The cranial cavity was opened and the brain, pituitary, and adjacent cervical tissues were examined. The skin was reflected from the carcass, and the thoracic and abdominal cavities were exposed and the viscera was examined in situ. All visceral tissues were dissected from the carcass and re-examined, including cut surfaces. The brain, heart, kidneys, liver, adrenal glands, ovaries, and testes were weighed. For the 1000 mg/kg/day male rats sacrificed on day 118, a complete set of tissues was collected, but no organ-weight data were generated since no control males were sacrificed at the same time. At the terminal sacrifice, microscopic examinations were performed on all collected tissues [except auditory sebaceous glands and bone joint] from all male rats of the control and 500 mg/kg/day dose groups and all female rats of the control and 1000 mg/kg/day dose groups. To the extent possible, a complete set of tissues was examined from all rats removed from the study. The lungs, liver, kidneys, and gross lesions were processed for histologic examination from rats of both sexes at the lower dose levels also. The adrenal gland was examined also in the lower-dose females because of an apparent treatment-related effect detected microscopically in the adrenal glands at the high-dose level. For the 1000 mg/kg/day males removed from the study on day 118, only the kidneys were examined microscopically from all 60 rats.

7

X	DIGESTIVE SYSTEM	X	CARDIOVASC./HEMAT.	X	NEUROLOGIC
X	Tongue	X	Aorta	X	Brain♣
X	Salivary glands	X	Heart	X	Periph.nerve [sciatic]
X	Esophagus	X	Bone marrow	X	Spinal cord♬
X	Stomach	X	Lymph nodes/tissue♦	X	Pituitary
X	Duodenum	X	Spleen	X	Eyes
X	Jejunum	X	Thymus		
X	Ileum				GLANDULAR
X	Cecum		UROGENITAL	X	Adrenal gland
X	Colon	X	Kidneys	X	Lacrimal/Harderian gland
X	Rectum	X	Urinary bladder	X	Mammary gland
X	Liver	X	Testes	X	Parathyroids
	Gall bladder	X	Epididymides	X	Thyroids
X	Pancreas	X	Prostate		
		X	Seminal vesicle		OTHER
	RESPIRATORY	X	Coagulating gland	X	Bone [w/joint]
X	Trachea	X	Ovaries	X	Skeletal muscle
X	Lung	X	Uterus	X	Skin
X	Nose	X	Vagina	X	Oral tissue
	Pharynx	X	Cervix	X	Auditory sebaceous gland
X	Larynx	X	Oviduct	X	All gross lesions and masses

♦ mesenteric & mediastinal; ♣ cerebrum, brainstem, cerebellum; ♬ cervical, thorax, lumbar

II. RESULTS

A. Observations

1. Toxicity - During the second half of the study, perineal soiling was observed in treated rats, which was not considered toxicologically significant but possibly due to the large quantity of fluroxypyr in the urine resulting in the lack of adequate preening of the urogenital area [Table 1]. There were an increased number of 1000 mg/kg/day females that were described as thin prior to removal from the study due to moribundity or death.

Table 1. In-Life Observations

Sex/Dose	0 mg/kg/day	100 mg/kg/day	500 mg/kg/day	1000 mg/kg/day
MALES				
perineal soiling				
12 month n=10	1	0	1	0
24 month n=50	7	12	13	-
FEMALES				
perineal soiling				
12 month n=10	0	5	3	8
24 month n=50	7	17	28	27
FEMALES n=50				
thin	6	5	2	24

data from Tables 10 & 11, pages 93-95 of the report

2. Mortality - **Males**: Two of the 50 males at the 1000 mg/kg/day dose level died during the first 4 weeks on test. Three more males in this group died during the next 4 weeks on test. On day 118 of the study, all males in this group were sacrificed. There was a dose-related increase in the % mortality, although statistical significance was not

attained. The first death at the 500 mg/kg/day dose level occurred during the 60-64 week interval, and by study termination, death had occurred in 40% of this group. For the low-dose and control groups, the first deaths occurred during the 56-60 week and 68-72 week intervals, respectively, and deaths had occurred in 30% and 24%, respectively, by study termination [Table 2]. **Females**: Females of the concurrent control were noted to have a low rate of mortality compared to recent historical control data [6/50 compared to 10/50, 25/50, 11/50, 15/50, and 7/50 in recent studies at the testing facility]. The first female rat to die on test was a control female [day 26], but the mortality rate in this group was only 12% [Table 2]. The high-dose females displayed a significant increase in mortality [42%] compared to the concurrent control, and the increase was considered to be treatment-related. There was no apparent adverse effect on survival in the low- and mid-dose females. The most frequent cause of death of the 1000 mg/kg/day females was renal failure [10 out of 21, resulting in starvation in 9 of these 10]. Renal failure was not a cause of death in the other groups.

Table 2. Mortality [# deaths/# rats in group (%)]

Sex/Dose	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
MALES	12/50 (24)	15/50 (30)	20/50 (40)	50♪/50 (100)
FEMALES	6/50 (12)	14/50 (28)	10/50 (20)	21/50* (42)

♪ 6/50 had died by day 112 and remaining were sacrificed on day 118; * $\alpha<0.05$; data from Tables 7 & 8, pages 90-91 of the report

B. Body weight - MALES Body weights [Table 3] of the high-dose males were decreased significantly from day 6 on, compared to the control males [90-97% of control]. On day 90, the high-dose male body weight was 90% of the control value. Body-weight gains [Table 4] fluctuated throughout the study at the high dose, with gains sometimes greater than those of the controls. The high-dose males gained less weight than the control [81% of control] and other treatment groups [group terminated on day 118]. TB II notes that a lower body-weight gain [91% of control] occurred in the high-dose males during the week prior to dosing also. FEMALES Body weight was comparable among the groups throughout the first year of the study [Table 3]. During the last quarter of the study, significant decreases in body weight were observed at the high dose [73-89% of control]. Body-weight gain was slightly lower [97% of control] than the controls in the females at the high-dose level during the first 90 days [Table 4], but overall, high-dose females displayed a decreased [69% of control] body-weight gain compared to the controls.

Table 3. Body Weight [% of control]

Day/Sex/Dose	100 mg/kg/day	500 mg/kg/day	1000 mg/kg/day
MALES			
pre-test -9	100	100	100
pre-test -2	98	98	98
6	99	99	97*
13	99	101	95*
20	99	100	94*
27	99	101	95*
34	99	101	95*
41	99	101	93*
76	98	100	91*
90	98	100	90*
366	98	98	-
562	96*	97*	-
730	99	96	-
FEMALES			
pre-test -9	100	100	100
pre-test -2	100	100	100
6	100	98*	97*
13	99	99	98
20	99	98	97*
27	99	98	97*
34	98	99	97*
41	99	98*	97*
76	98*	98	97*
90	99	99	99
366	98	98	94*
562	98	98	89*
646	101	99	74*
702	99	99	73*
730	99	100	81*

* α $p<0.05$ [either Dunnett's or Wilcoxon's test; data from Tables 16-17 [pages 108-113 of the report]

Table 4. Body-Weight Gain♬ [grams (% of control)]

Interval⧖/Sex/Dose	0 mg/kg/day	100 mg/kg/day	500 mg/kg/day	1000 mg/kg/day
MALES				
pre-test	34.6	31.4	31.9	31.5 [91]♪
-2-6	29.0	29.9	30.6	25.7* [89]
-2-13	51.2	52.8	55.4*	43.3* [85]
-2-20	67.6	68.0	71.1	56.2* [83]
-2-41	104.0	104.4	109.7	88.1* [85]
-2-90	154.6	151.9	158.2	125.9* [81]
-2-366	258.9	253.1	252.8	-
-2-730	210.0	210.1	197.8	-
6-13♬	22.1	22.8	24.9	17.7 [80]
13-20♬	16.4	15.3	15.7	12.9 [79]
20-27♬	14.8	15.0	16.0	17.6 [119]
FEMALES				
pre-test	16.6	16.6	16.4	16.6
-2-6	16.8	16.4	14.1* [84]	13.4* [80]
-2-13	28.5	27.7	27.7	26.1* [92]
-2-20	38.0	36.6*	36.1* [95]	34.2* [90]
-2-41	58.8	56.5	55.9* [95]	53.5* [91]
-2-90	81.5	79.4	80.1	79.4 [97]
-2-366	118.7	114.3	115.2	106.0* [89]
-2-730	168.2	165.2	169.3	115.5* [69]
6-13♬	11.7	11.3	13.6	12.7
13-20♬	9.5	8.9 [94]	8.4 [88]	8.1 [85]
20-27♬	10.1	9.4 [93]	9.7 [96]	8.9 [88]

⧖ days; ♪ [% of control]; * $\alpha<0.05$; ♬ calculated by reviewer using data from Tables

10

16-17 [pages 108-113] of report; data from Tables 18-19 [pages 114-125] of the report

C. Food consumption/efficiency - **MALES** There were no adverse effects on food consumption or food efficiency at any dose level during the first 12 weeks of the study. During the day 85-92 interval, food consumption at the high dose was slightly lower [93% of control] than the control, but the last interval measured [days 106-113] was 96% of the control value [high dose sacrificed on day 118]. **FEMALES** Food consumption and food efficiency were comparable among the groups.

D. Ophthalmoscopic examination - There were no treatment-related findings in either sex at any dose level.

E. Clinical Pathology - HEMATOLOGY **MALES**: At 13 weeks, slight decreases were observed in hemoglobin, hematocrit, and red blood cell values at the high dose compared to the controls [Table 5]. Total WBC counts were slightly increase at the high-dose level at 13 weeks, and examination of the differential WBC counts in these rats showed an increase in the percent of segmented neutrophils [evidence of inflammation] and an increase in nucleated RBC [indicative of a regenerative anemia]. Additionally, red blood cell hypochromasia [5 of 15 examined] and polychromasia [3 of 15 examined] were observed at the high dose at 13 weeks. It was concluded that these changes were due to the overall poor condition of these rats and minimally to renal damage. There were no apparent treatment-related effects on these parameters at the other two dose levels, although the 500 ppm dose group displayed the lowest values for the erythroid parameters, and the total WBC counts were elevated at 24 months compared to the control value. Morphology was comparable among the groups at study termination. **FEMALES**: The high-dose group [1000 mg/kg/day] displayed slightly decreased RBC, hemoglobin, and hematocrit values compared to the control values throughout the study [Table 6]. The low dose displayed significant increases in RBC and hemoglobin at the 13-week and 18-month intervals. Increased platelet counts were observed at the high-dose level throughout the study, with statistical significance being attained at 6, 18, and 24 months. There was a decrease in total WBC counts at all dose levels [no dose response] at 24 months [statistically significant at the high dose], and this was attributed to fewer high-dose rats with an altered WBC due to Fischer rat leukemia compared to the controls. The hematocrit at the high-dose level was decreased and the platelet counts were increased. No morphologic changes of the blood were considered treatment-related. The decreases in erythroid parameters observed were attributed to decreased nutritional state, lower body weights, and progressive nephropathy and considered to be secondary to other disease processes and not to bone marrow toxicity.

Table 5. Hematology Parameters - MALES

Parameter/Dose♦/Time	13 weeks	6 months	12 months	18 months	24 months
HGB [G/DL]					
0	15.6 {0}	16.3	14.5	15.8	13.6
100	15.7 {0}	16.3	14.8	15.5	13.8
500	15.7 {1}	15.9	14.2	15.2	13.2
1000	15.2 {3}	-	-	-	-
RBC [x10^6/mm^3]					
0	10.62	9.59	9.04	9.02	7.59
100	10.66	9.66	9.16	8.84	7.68
500	10.75	9.39	8.84	8.61 [95]	7.28 [96]
1000	10.15 [96]♪	-	-	-	-
HCT [%]					
0	58.8	59.1	56.0	46.7	38.5
100	59.3	59.6	56.8	45.8	38.6
500	59.2	57.9	54.4	44.9 [96]	36.9 [96]
1000	56.8 [97]	-	-	-	-
WBC [x10^6/mm^3]					
0	5.2	6.2	5.4	5.84	7.62
100	5.6	6.7	5.0	6.00	8.65 [114]
500	5.7 [110]	6.7	5.2	5.41	10.19 [134]
1000	6.1 [117]	-	-	-	-

♦ mg/kg/day; - no data; ♪ [% of control]; {# of rats w/ value < 15}; data from Tables 24-28, pages 136 to 160 of the report

Table 6. Hematology Parameters - FEMALES

Parameter/Dose♦/Time	13 weeks	6 months	12 months	18 months	24 months
HGB [G/DL]					
0	15.1 {2}	15.7	15.2	15.6	14.6
100	15.6* {0}	15.6	14.9	16.2*	14.9
500	15.2 {2}	15.3	14.9	15.6	15.1
1000	14.9 {6}	15.3	14.4	15.4	13.5 [92]♪
RBC [x10^6/mm^3]					
0	9.63	8.52	8.49	8.54	7.77
100	9.91*	8.34	8.45	8.76*	7.97
500	9.74	8.32	8.31	8.52	8.29
1000	9.52	8.20 [96]	8.07* [95]	8.42	7.32 [94]
HCT [%]					
0	57.6	57.1	57.5	45.7	40.2
100	59.1	55.5	56.7	47.4*	40.9
500	58.1	55.5	56.1	45.5	41.2
1000	56.9	54.5* [95]	54.3* [94]	44.8	37.1* [92]
WBC [x10^6/mm^3]					
0	4.4	3.9	3.3	3.36	6.52
100	4.6	4.2	3.4	2.92 [87]	5.31 [81]
500	4.5	4.3	3.2	3.02 [90]	3.89 [60]
1000	4.7 [107]	4.6* [118]	3.4	3.33	4.97* [76]
platelets [[x10^6/mm^3]					
0	423	634	568	570	499
100	421	644	544	587	570
500	439	642	607	628	572
1000	438 [104]	707* [112]	620 [109]	648* [114]	646* [129]

♦ mg/kg/day; ♪ [% of control]; {# of rats w/ value < 15}; * α <0.05; data from Tables 29-33, pages 161-188 of the report

12

CLINICAL CHEMISTRY There were changes in several parameters that were consistent with kidney effects and/or nutritional state of the animal [Tables 7 & 8]. At 13 weeks, blood urea nitrogen and cholesterol values were increased at the 1000 mg/kg/day dose level in males, and decreases were observed in triglycerides. Blood urea nitrogen values were decreased at the 500 mg/kg/day level at 12 and 18 months in males, and males at this dose level and females at the 1000 mg/kg/day dose level displayed increases in this parameter at study termination, consistent with chemically-induced nephrotoxicity.

Table 7. Clinical Chemistry Parameters - MALES

Parameter/Dose♦/Time	13 weeks	6 months	12 months	18 months	24 months
urea nitrogen [MG/DL]					
0	20	18	16	16	21
100	18	19	15	16	25
500	20	18	15*	14* [88]♦	38* [181]
1000	33	-	-	-	-
CHOL [MG/DL]					
0	65	83	99	154	183
100	68	81	92	154	196
500	68	78	84	150	177
1000	81 [125]	-	-	-	-
TRIG [MG/DL]					
0	131	190	137	157	194
100	128	190	143	128	235
500	150	173 [91]	115 [84]	123 [78]	190 [98]
1000	116	-	-	-	-
Total Protein [G/DL]					
0	7.8	7.9	6.9	7.7	7.1
100	7.8	7.8	6.9	7.4	7.0
500	7.8	7.6	6.8	7.3* [95]	7.0
1000	7.5	-	-	-	-
Creatinine MG/DL					
0	0.7	0.7	0.7	0.7	0.8
100	0.7	0.7	0.6	0.7	0.9
500	0.7	0.7	0.7	0.7	1.0
1000	0.8	-	-	-	-
ALT [MU/ML]					
0	39	56	83	38	44
100	38	51	89	43	41
500	39	51	71	33	57
1000	41	-	-	-	-
AP [MU/ML]					
0	77	68	65	51	68
100	81	70	63	50	74
500	81	66	61	44	86
1000	79	-	-	-	-
AST [MU/ML]					
0	77	95	126	78	100
100	73	90	138	82	112
500	69	88	116	73	135
1000	82	-	-	-	-

♦ [% of control]; data from Tables 34-88, pages 189 to 202 [males] and Tables 28-33, pages 161-188 of the report

13

Table 8. Clinical Chemistry Parameters - FEMALES

Parameter/Dose♦/Time	13 weeks	6 months	12 months	18 months	24 months
urea nitrogen [MG/DL]					
0	18	20	15	17	16
100	18	20	16	16	17
500	16	20	16	17	17
1000	17	20	14	15	27* [169]
CHOL [MG/DL]					
0	109	130	132	158	161
100	115	125	134	155	189
500	117	132	140	161	167
1000	112	125	127	150	188
TRIG [MG/DL]					
0	64	67	72	124	206
100	63	71	61	133	255
500	60	73	61	126	184
1000	63	67	51*	119	211
Total Protein [G/DL]					
0	8.2	8.0	7.1	8.1	7.8
100	8.3	7.8	7.2	8.0	7.7
500	8.1	8.0	7.4	8.2	7.8
1000	8.0	7.6* [95]♦	7.2	8.1	7.5
Creatinine [MG/DL]					
0	0.8	0.8	0.6	0.7	0.7
100	0.8	0.8	0.6	0.7	0.7
500	0.7	0.7	0.6	0.7	0.7
1000	0.8	0.7	0.6	0.7	0.9*
ALT [MU/ML]					
0	37	46	47	40	49
100	42	41	48	39	49
500	38	40	44	34	49
1000	37	41	37 [79]	39	44 [90]
AP [MU/ML]					
0	58	46	31	36	54
100	59	46	30	43	61
500	57	46	31	40	46
1000	63	48	33	42	57
AST [MU/ML]					
0	76	81	80	75	108
100	82	75	89	73	109
500	77	77	84	72	98
1000	78	78	72	73	76

♦ [% of control]; data from Tables 34-88, pages 189 to 202 [males] and Tables 38-43, pages 203-218 of the report

URINALYSIS At the 1000 mg/kg/day dose level, specific gravity was decreased in both sexes at 13 weeks. At 6 months, males at the mid-dose level and females at the high-dose level displayed decreased specific gravity, and both the mid- and high-dose females displayed decreased specific gravity values at 12 and 18 months. At 24 months, the high-dose females still had decreased specific gravity values. Urine pH was lower than the control in both sexes throughout the study at the mid- and high-dose [females] levels; i.e., fewer treated rats had pH values ≥7. Additionally, rats at the mid- and high-dose levels of both sexes had less protein and ketones in the urine than the control rats.

14

Table 9. Urinalysis Parameters - BOTH SEXES

Parameter/Dose♦/Time	13 weeks	6 months	12 months	18 months	24 months
Specific gravity					
MALES					
0	1.053	1.059	1.052	1.055	1.040
100	1.053	1.060	1.054	1.056	1.040
500	1.045	1.052*	1.052	1.053	1.030
1000	1.024*	-	-		-
FEMALES					
0	1.050	1.050	1.051	1.050	1.033
100	1.047	1.050	1.045	1.044	1.032
500	1.045	1.048	1.042*	1.042*	1.027
1000	1.032*	1.033*	1.034*	1.038*	1.025*
Ph					
MALES					
0	6.7	7.0	7.15	6.7	7.15
100	7.15	6.8	7.3	6.55	6.9
500	6.55	6.25	6.9	5.9	6.45
1000	5.8	-	-	-	-
FEMALES					
0	7.15	7.25	7.45	6.85	6.8
100	6.75	7.45	7.35	7.05	7.1
500	6.3	6.85	6.55	6.2	6.55
1000	5.8	6.5	6.2	6.0	6.25
Protein [MG/DL]					
MALES					
0	7+,3++	5++, 5+++	1-, 1+, 2++, 6+++	10+++	1+, 2++, 7+++
100	6+, 3++, 1+++	5++, 5+++	2-, 1+, 1++, 6+++	1++, 9+++	10+++
500	9+,1++	5+, 5++	1-, 2++, 7+++	6++, 4+++	2+, 1++, 7+++
1000	4-, 7tr, 4+	-	-	-	-
FEMALES					
0	1tr, 9+	1-, 1tr, 8+	6+, 3++, 1+++	1-, 3++, 6+++	3+, 3++, 4+++
100	3tr, 7+	1tr, 8+, 1++	1-, 1tr, 4+, 2++, 2+++	4+, 3++, 3+++	2++, 8+++
500	2-, 7tr, 1+	2-, 6tr, 2+	1tr, 8+, 1++	4+, 5++, 1+++	2+, 4++, 4+++
1000	7-, 2tr, 1+	10-	7-, 2tr, 1++	3-, 1tr, 4+, 2++	1-, 2+, 4++, 3+++
Ketones [MG/DL]					
MALES					
0	1-, 9+	1tr, 9+	8tr, 2+	2-, 8tr	6-, 4tr
100	10+	2tr, 8+	1-, 7tr, 2+	1-, 9tr	7-, 3tr
500	2-, 4tr, 4+	1-, 6tr, 3+	1-, 9tr	4-, 6tr	9-, 1tr
1000	14-, 1tr	-	-	-	-
FEMALES					
0	7-, 3+	8-, 2tr	6-, 4tr	6-, 4tr	6-, 4tr
100	8-, 2tr	5-, 5tr	7-, 3tr	8-, 2tr	8-, 2tr
500	10-	10-	10-	10-	9-, 1tr
1000	9-, 1tr	10-	10-	10-	10-

data from Tables 44-53, pages 219-242 the report; - negative; tr trace; + slight, ++ moderate, +++ severe; * α=0.05

G. Sacrifice and Pathology - **INTERIM SACRIFICE** MALES: At the 12-month sacrifice, final [fasted] body weights were slightly [93% of control] lower at the 500 mg/kg/day dose level than the control. FEMALES: A statistically significant decrease was observed in terminal [fasted] body weight at all dose levels, but the decrease at the 100 and 500 mg/kg/day dose levels was unrelated to treatment. In comparing the body weights for day 366 [last weight prior to the 12-month (chronic phase) sacrifice] of the two phases of the study, the designated 10 female controls of the chronic phase of the study are ≈13 grams heavier than the controls of the cancer phase. Comparing the 2 phases for the 100 and

500 mg/kg/day groups shows that they are within 3-7 grams [Table 10]. When the body weight from both phases [day 366] are combined, only the high-dose group shows a significant decrease in body weight compared to the control. It is concluded that only the decrease in body weight at the high dose is real. **FINAL SACRIFICE** MALES: At the 500 mg/kg/day dose level, there was a slight decrease [94% of the control] in body weight at the final sacrifice. FEMALES: There was a significant decrease [80% of control] in body weight at study termination at the high [1000 mg/kg/day] dose [Table 11].

Table 10. Comparison of Body-Weight Data for Interim and Final Sacrifice Rats - Males

Body Weight/Dose [mg/kg/day]	0	100	500	1000
[Interim] Chronic Phase n= mean body weight (g) [day 366]	10 232.9	10 215.9	10 219.4	10 218.6
Cancer Phase n= mean body weight (g) [day 366]	49 220.1	50 222.9	50 222.9	49 212.2
difference between phases (g)	12.7	7.0	3.5	6.4
Combined n= mean body weight (g) [day 366]	59 226.0	60 221.7	60 222.3	59 213.4*
[Interim] Chronic Phase n= mean fasted body weight (g)	10 212.0	10 190.7*	10 198.8*	10 199.6*

data from page 57 of the report

1. Organ weight - **INTERIM SACRIFICE** MALES: With the exception of the kidney, the slight decreases in organ weights noted at the 500 mg/kg/day dose level are consistent with the slightly decreased body weight of this group compared to the controls. The absolute kidney weight of the 500 mg/kg/day males was slightly higher [102% of the control] than the control, and the relative kidney weight was significantly higher [110% of control] than the control. FEMALES: Absolute organ weights were all slightly increased at the high-dose level at 12 weeks, although body weight for this group was slightly decreased [94% of control] and consequently, all relative organ weights were increased. At study termination, the mid- and high-dose females displayed significantly increased absolute and relative ovarian weights [dose-related]. Increased absolute and relative adrenal and kidney weights were observed at all dose levels, but only the relative weights displayed a dose response. The significant decrease in absolute heart weight and increase in relative heart weight may be attributed to the decreased body weight [Tables 11 and 12].

Table 11. Organ-Weight Data [Absolute]

Organ/Dose♦/Sex	Final BW	adrenals	brain	heart	kidneys	liver	testes/ovaries
INTERIM MALES							
0	400.7	0.046	1.995	1.099	2.439	10.353	3.334
100	395.1	0.045	2.020	1.096	2.476	10.127	3.334
500	372.6 [93]♪	0.045	1.980	1.055 [96]	2.486 [102]	9.708 [94]	3.253
INTERIM FEMALES							
0	212.0	0.054	1.856	0.740	1.536	5.579	0.047
100	196.7* [93]	0.054	1.826	0.714	1.484	5.324	0.042
500	198.8* [94]	0.056	1.865	0.732	1.559	5.632	0.045
1000	199.6* [94]	0.059 [109]	1.884 [102]	0.760 [103]	1.668 [109]	6.028 [108]	0.048 [102]
FINAL MALES							
0	353.3	0.079	2.120	1.143	2.859	10.473	5.511
100	347.0	0.077*	2.095	1.066	3.043	11.226	5.852
500	333.7 [94]	0.075	2.106	1.043	3.209* [112]	11.042	5.893
FINAL FEMALES							
0	257.2	0.069	1.898	0.818	1.972	7.162	0.060
100	256.0	0.073 [106]	1.897	0.834	2.128* [108]	7.534	0.064
500	258.1	0.088 [128]	1.929	0.839	2.286* [116]	7.408	0.071*
1000	206.4* [80]	0.076 [110]	1.931 [102]	0.772* [94]	1.990 [101]	6.925	0.087 [145]

♦ mg/kg/day; ♪ [% of control]; * p or α <0.05; data from Tables 54-57 [pages 243-246] of the report

Table 12. Organ-Weight Data [Relative]

Organ/Dose♦/Sex	Final BW	adrenals	brain	heart	kidneys	liver	testes/ovaries
INTERIM MALES							
0	400.7	0.0116	0.500	0.275	0.609	2.583	0.832
100	395.1	0.0116	0.513	0.278	0.628	2.563	0.847
500	372.6	0.0122 [105]♪	0.533 [107]	0.284 [103]	0.668* [110]	2.607	0.876
INTERIM FEMALES							
0	212.0	0.0255	0.877	0.349	0.726	2.630	0.022
100	196.7*	0.0275	0.929* [106]	0.363 [104]	0.755	2.705	0.022
500	198.8*	0.0280	0.939* [107]	0.368 [105]	0.785* [108]	2.836* [108]	0.023
1000	199.6*	0.0294	0.946* [108]	0.381* [109]	0.836* [115]	3.014* [115]	0.024 [109]
FINAL MALES							
0	353.3	0.0226	0.603	0.333	0.814	2.985	1.556
100	347.0	0.0225	0.609	0.310	0.885 [109]	3.270 [110]	1.689 [109]
500	333.7	0.0226	0.639	0.315	0.972* [119]	3.335* [112]	1.727 [111]
FINAL FEMALES							
0	257.2	0.0272	0.747	0.321	0.774	2.805	0.024
100	256.0	0.0289 [106]	0.752	0.329	0.841* [109]	2.958 [105]	0.025
500	258.1	0.0344 [128]	0.753	0.327	0.892* [115]	2.877* [103]	0.028* [117]
1000	206.4* [80]	0.0374* [110]	0.949* [127]	0.379* [118]	0.974* [126]	3.391* [121]	0.045* [188]

♦ mg/kg/day; ♪ [% of control]; * p or α <0.05; data from Tables 54-57 [pages 243-246] of the report

The historical control data for mean body weight and absolute and relative kidney weights were provided for female Fischer 344 rats from 5 recently conducted chronic studies conducted at the testing facility [Table 13]. The absolute kidney weights observed at the low- and mid-dose levels in females are outside [greater than] the historical control [HC] range. The value at the high-dose level is within the historical range but this group's body weight is well below [206.4 grams] the HC range. With respect to the relative kidney weight, only the low dose value is within the HC range.

Table 13. Historical Control Data on Kidney Weight

Body Weight [g]	Absolute Kidney Weight [g]	Relative Kidney Weight [g/100 g]
235.8 to 265.8	1.878 to 2.038	0.717 to 0.844

data from page 60 of the report

2. Gross pathology - MALES: At the 1000 mg/kg/day dose level, which was terminated at day 118, the kidneys were noted to be decreased in size [any symmetry] in ≈38%, roughened surface was noted in ≈72%, and necrosis of the papilla(e) was observed in ≈12% of these rats [Table 14]. Additionally, a third of these rats were noted to have a decreased amount of fat. At the 100 and 500 mg/kg/day dose levels, there were no treatment-related effects in the kidneys or other organs/tissues at necropsy. At study termination, decreased amount of fat was noted in the treated rats at both dose levels compared to the controls. In the kidney, roughened surface was displayed, and in the stomach erosion and/or ulcer was observed more frequently at the 500 mg/kg/day dose level than in the control. All other findings were comparable among the groups. FEMALES: At the 12-week sacrifice, one of 10 high-dose females showed a decrease in the amount of fat. All other findings at necropsy were comparable among the groups of females. At study termination, decreased amount of fat was observed in the high-dose females compared to the control and other groups. In the kidneys, decreased size and roughened surface were noted most frequently at the high dose. Erosion and/or ulcer(s) of the glandular mucosa of the stomach was observed most frequently at the high dose.

Table 5. Gross Pathology Findings

Organ/Finding/ Dose [mg/kg/day]/ Sex/Interval	MALES		FEMALES	
	12-month	final	12-month	final
Kidney - roughened surface				
0	0	9/50	0	0
100	0	2/50	0	0
500	-	17/50	0	7/50
1000 [♂♂ day 118]	43/60	-	0	32/50
Kidney - decreased size				
0	0	0	0	0
100	0	0	0	0
500	0	0	0	0
1000 [♂♂ day 118]	23/60	-	0	10/50
Kidney - papillary necrosis				
0	0	0	0	0
100	0	0	0	0
500	0	0	0	0
1000 [♂♂ day 118]	7/60	-	0	0
General - decreased amount of fat				
0	0	6/50	0	3/50
100	0	11/50	0	7/50
500	0	15/50	0	1/50
1000 [♂♂ day 118]	18/60	-	1/10	24/50
Stomach - erosion/ulcer, glandular mucosa				
0	0	5/50	0	3/50
100	0	7/50	0	2/50
500	0	11/50	0	2/50
1000 [♂♂ day 118]	5/60	-	0	10/50

- no data; data from Tables 59, 61, 64 [pages 249-251, 253-255, and 273-292 of the report

3. Microscopic pathology - The major target organ for Fluroxypyr appears to be the kidney.

a) Non-neoplastic - **KIDNEY** In the 1000 mg/kg/day males removed from the study on day 118, hyperplasia of the pelvic epithelium, papillary necrosis, and tubular nephrosis were observed. It was stated that these changes would not be expected in rats of this age, and the findings were attributed to treatment, although there were no concurrent controls examined at this time point. There were no apparent treatment-related lesions observed in either sex at the 12-month sacrifice, although one male at the 500 mg/kg/day dose level and one female at the 1000 mg/kg/day dose level displayed an increase in severity of the background degeneration/regeneration of the kidney tubules. At study termination, the number of 500 mg/kg/day males displaying chronic progressive glomerulonephropathy [CPG] identified at a severe or very severe degree was greater than that in the control and low dose and stated to be greater than the historical control. In the high-dose females at study termination, there was an increase in the incidence and severity of renal CPG, an increase in the number with focal mineralized deposits with associated hyperplasia of the renal pelvic epithelium, and a slight increase in pigment in the epithelial cells, which were undergoing degenerative change. The increases in mineralization and pigmented

tubules were considered to be secondary effects of renal disease and the associated generalized decreased nutritional state of these rats. It was stated that the absence in these rats of extensive mineralization in kidney basement membranes and other tissues was unusual for rats with terminal renal failure. **ALL OTHER ORGANS/TISSUES** Females at the high-dose level displayed hypertrophy of the zona glomerulosa of the adrenals and an increased incidence of erosion/ulcers of the glandular mucosa compared to the controls. The lesion in the adrenal was not associated with an increase in the mean absolute adrenal weight and was noted more often in females with the more advanced stages of renal disease. Males at the 500 mg/kg/day dose level and females at the 1000 mg/kg/day dose level displayed an increased incidence of atrophy of the adipose tissue compared to the controls. The female control rats displayed a higher incidence of focus(i) of altered cells in the adrenal cortex, degeneration with or without inflammation of the heart, inflammation of the lacrimal gland, focus(i) of altered cells [hepatocellular], strangulated or necrotic fat in the mesenteric tissues, parafollicular cell hyperplasia of the thyroids, and endometrial stromal polyps than the high-dose females. Control males displayed a higher incidence of mineralization in the larynx, focus(i) of altered cells [hepatocellular], and pigment in the pituitary than the treated males [Table 15].

24

Table 15. Microscopic Observations - Non-neoplastic [all rats]

Lesion/Sex/Dose [mg/kg/day]	0	100	500	1000
MALES				
KIDNEY n=50				
chronic progressive glomerulonephropathy - unilateral				
severe	0	0	0	-
very severe	0	0	1	-
chronic progressive glomerulonephropathy - bilateral				
very slight	12	15	9	-
slight	21	14	14	-
moderate	13	17	17	-
severe	4	2	8	-
very severe	0	2	1	-
chronic progressive glomerulonephropathy - unilateral/bilateral				
severe and very severe	4	4	10	-
chronic progressive glomerulonephropathy - any symmetry				
any severity	50	50	50	-
hyperplasia, pelvic epithelium - unilateral				
very slight	5	1	1	-
slight	0	0	0	-
hyperplasia, pelvic epithelium - bilateral				
very slight	0	0	0	-
slight	0	1	0	-
hyperplasia, pelvic epithelium - any symmetry				
any severity	5	2	1	-
mineralization, pelvic epithelium - unilateral				
very slight	10	10	10	-
slight	0	0	0	-
mineralization, pelvic epithelium - bilateral				
very slight	8	2	11	-
slight	0	0	0	-
mineralization, pelvic epithelium - any symmetry				
any severity	18	12	21	-
pigment, tubule - bilateral				
very slight	24	22	26	-
slight	21	21	19	-
moderate	5	5	4	-
severe	0	0	0	-
any severity	50	48	49	-

Table 15. Microscopic Observations - Non-neoplastic [all rats]

Lesion/Sex/Dose [mg/kg/day]	0	100	500	1000
FEMALES				
KIDNEY n=50				
chronic progressive glomerulonephropathy - unilateral				
severe	0	0	1	2
very severe	0	0	0	9*
chronic progressive glomerulonephropathy - bilateral				
very slight	35	41	35	8*
slight	13	7	10	12
moderate	2	2	3	14*
severe	0	0	1	4
very severe	0	0	0	1
chronic progressive glomerulonephropathy - unilateral/bilateral				
severe and very severe	0	0	2	16*
chronic progressive glomerulonephropathy - any symmetry				
any severity	50	50	50	50
hyperplasia, pelvic epithelium - unilateral				
very slight	10	2	3	6
slight	1	0	0	0
hyperplasia, pelvic epithelium - bilateral				
very slight	2	0	4	10*
slight	0	0	0	1
hyperplasia, pelvic epithelium - any symmetry				
any severity	13	2*	7	17
mineralization, pelvic epithelium - unilateral				
very slight	12	6	15	16
slight	1	0	1	0
mineralization, pelvic epithelium - bilateral				
very slight	11	4*	13	23*
slight	0	0	0	1
mineralization, pelvic epithelium - any symmetry				
any severity	24	10*	29	40*
pigment, tubule - bilateral				
very slight	25	18	34	9*
slight	18	26	14	29*
moderate	5	4	2	6
severe	1	1	0	2
any severity	49	49	50	46
FEMALES				
ADRENALS n=50				
hypertrophy, zona glomerulosa - bilateral				
very slight	0	0	0	14*
slight	0	0	0	17*
any severity	0	0	0	31*
FEMALES				
STOMACH n=	50	15	10	50
erosion(s) and/or ulcer(s), glandular mucosa				
focal	3	1	2	6
multifocal	2	3	1	8*
focal or multifocal	5	4	3	14*
MALES				
MESENTERIC TISSUES n=	50	20	50	-
atrophy, adipose tissue	10	12	21*	-
FEMALES				
MESENTERIC TISSUES n=	50	23	14	50
atrophy, adipose tissue	8	9	2	31*
FEMALES				
LIVER n=50				
hepatocellular atrophy [secondary to inanition]	2	6	5	14*

* $\alpha<0.05$ [Yate's Chi-square pairwise test]; data from Table 65 [pages 293-341] of the report; - no data

b) Neoplastic lesions: There was no apparent increase in the incidence of any tumor type in either sex [Table 16]. Males at the 500 mg/kg/day

dose level displayed a slight increase in parafollicular cell adenomas of the thyroid compared to the control incidence. It is to be noted that this increase is observed only for single adenomas; when the incidence of two adenomas in one rat is added to the single adenoma rats, the increase is not significant. The tumor incidence table of the report [Table 66; pages 342-350] is appended to the file copy of the DER.

Table 16. Microscopic Observations - Neoplastic [all rats]

Lesion/Sex/Dose [mg/kg/day]	0	100	500	1000
MALES				
THYROID n=50				
adenoma, parafollicular cells, benign, primary [1]	4/50	1/17	11*/50	-
adenoma, parafollicular cells, benign, primary [>1]	1/50	0/17	0/50	-
adenoma, parafollicular cells, benign, primary [combined]	5/50	1/17	11/50	-
combined adenoma and carcinoma, parafollicular	6/50	3/17	11/50	-
carcinoma, follicle(s), malignant, primary, no metastasis	2/50	0/17	0/50	-

* $\alpha<0.05$ Yate's Chi-square pairwise test; data from Table 66 [pages 342-350] of the report

III. DISCUSSION

A. Following oral exposure of Fischer 344 rats to Fluroxypyr via the diet at dose levels up to 1000 mg/kg/day for 24 months, the kidney was found to be the major target organ in both sexes. Males were more sensitive than females, and during the first 13 weeks of the study, erratic growth, mortality, and moribundity were observed in males at the 1000 mg/kg/day dose level. This group was terminated on day 118 of the study. Body weight of the high-dose males was decreased throughout the study, and by day 90 was 90% of the control value. Body-weight gain during the first 3 weeks of dosing ranged from 83% to 89% of the control values. Food consumption for this group was comparable to the control. Gross examination of these males showed excessive renal toxicity [decreased size of kidney (38%), papillary necrosis (12%), roughened surface (72%)]. Females at the high-dose level also displayed an increase in mortality, with the most frequent cause of death being renal failure [48% of the deaths]. There were no adverse effects on survival at the other dose levels in either sex. Decreased body weight [73-94% of control] was observed in the high-dose females throughout the study, especially after 90 days on test, and body-weight gains were decreased [69% of control overall] relative to the control also. Body weight/gain was not adversely affected at the low- and mid-dose levels in either sex. Hematology [↓ RBC, HGB, HCT], clinical chemistry [↑ BUN, CHOL], and urinalysis [↓ specific gravity, pH, proteins, ketones] values fluctuated throughout the study with no obvious target organ being identified. The changes noted were at times consistent with kidney effects and/or nutritional state of the rat. At the terminal sacrifice, the increases in kidney weight noted at 500 mg/kg/day in males was associated with microscopic renal toxicity [combined chronic progressive glomerulonephropathy]. At the final sacrifice, the high-dose females did not display a significant increase in absolute kidney weight but display an increased relative kidney weight, which was associated with hyperplasia and mineralization of pelvic epithelium and tubular pigment in the kidneys. In light of the low final body weight of the high-dose females [80% of control], the absolute kidney weight is considered to be increased also [101% of control]. Females at the low- [108% of control] and mid-dose [116% of control] levels also displayed a statistically

significant increase in kidney weight, which was noted by the author to be "in close proximity to historical controls" and not associated with changes in hematology, clinical chemistry, urinalysis, or histopathology indicative of renal toxicity. This reviewer notes that the values for both the absolute [low and mid] and relative [mid] kidney weights in the current study are outside [greater than] the historical control range. Microscopically, in addition to the histopathological lesions observed in the kidneys, hypertrophy in the zona glomerulosa of the adrenals was observed in the high-dose females, atrophy of the adipose tissue in both sexes at their respective high-dose levels, erosion and/or ulcer of the glandular mucosa of the stomach in high-dose females, and an increased incidence of parafollicular cell adenomas [single only] in males at 500 mg/kg/day. When the incidence of more than one parafollicular cell adenoma is added to the incidence of single adenomas, there is no significant increase observed. With respect to the adrenal, there was no increase in absolute adrenal weight associated with the increase in hypertrophy, and the lesion was most apparent in females with the more advanced stages of renal disease. In females at 1000 mg/kg/day, there was an increase in combined chronic progressive glomerulonephropathy, unilateral and bilateral [severe and very severe] and an increase in mineralization of the pelvic epithelium. There was no increase in the incidence of kidney tumors in either sex.

B. Study deficiencies: None that would adversely affect study interpretation. However, there are no succinct tables provided displaying the pertinent effects observed.

cc: LTaylor [RRB1]
7509C:RRB1:LTaylor:CM#2Rm816C:305-6486:8/6/97
RDI:CSwentzel:8/20/97:ToxTeam: / /97

Sign-off date: 09/29/97
DP Barcode: d232550
HED DOC Number: 012328
Toxicology Branch: tb2

26

Sign-off date: 09/29/97
DP Barcode: d232217
HED DOC Number: 012328
Toxicology Branch: tb2