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DATA EVALUATION RECORD

STUDY TYPE: Multigeneration Reproduction Study - [rat]
OPPTS 870.3800 [§83-4]

DP BARCODE: D232217
P.C. CODE: 128959

SUBMISSION CODE: S515138

ID #: 062719-EIL STARANE F
REGISTRATION CASE NO.: 060640
CASWELL NO.: 463 O
CAS Number: 81406-37-3
MOLECULAR FORMULA: $C_7H_5Cl_2FN_2O_3$

TEST MATERIAL (PURITY): Fluroxypyr

SYNONYMS: ((4-amino-3,5-dichloro-6-fluoro-2-pyridinyl)oxy)acetic acid
DOWCO*433#

CITATION: Vedula, U.; Quast, J.F.; and Breslin, W.J. (1996) FLUROXYPYR: Two-Generation Dietary Reproductive Toxicity Study in Sprague-Dawley Rats. The Toxicology Research Laboratory Health and Environmental Sciences, The Dow Chemical Company. Study ID: K-129976-012; June 19, 1996. MRID 44080321. Unpublished.

SPONSOR: DowElanco

EXECUTIVE SUMMARY: In a 2-generation reproduction study [MRID 44080321], Fluroxypyr [99.0% a.i.] was administered to 30 Sprague-Dawley rats/sex/dose via the diet at dose levels of 0, 100, 500, and 750 mg/kg/day [males] and 0, 100, 500, and 1000 mg/kg/day [females] during the pre-mating period of 10 weeks [F1 generation]/12 weeks [F2 generation]. There was one litter [F1] in the first generation and two litters [F2A and F2B] in the second generation. Treatment-related deaths due to renal failure occurred in both sexes at the high dose in both generations {1 P1 male [day 100], 2 P1 females [days 48 & 71], 1 P2 male [day 112], 1 P2 female [day 50]}. Males of both generations displayed lower body weights [P1 (91-94% of control); P2 (89-93% of control)] and body-weight gains [P1 (93%)/P2 (91% of control] during the dosing period and overall. Body weight and body-weight gain were comparable among the P1 females throughout the dosing period, but the P2 females displayed lower body weight [88-94% of control] and body weight gain [91% of control] during the dosing period. Food consumption was comparable among the P1 rats of both sexes during the dosing period, but decreased food consumption was noted in the P2 rats of both sexes. The effects observed increased progressively with time of exposure. During gestation, body weights were comparable among the P1 dams, and progressively lower than the controls at the high-dose level for the P2 dams during both gestation periods [1st 88-92% of control/2nd 86-91% of control]. Body-weight gains were progressively lower than the controls with each subsequent gestation period [P1 86%/1st P2 82%/2nd P2 74% of control]. During lactation, all dams of both generations displayed body weights that were initially lower than

control values but by day 21 of lactation were comparable to the control values. Body-weight gains during lactation were greater than the controls at the mid- and high-dose levels [dose-related] for both generations and both litters of the P2 generation, and this effect increased progressively with time of exposure. There were increases in kidney weight with corresponding gross and microscopic findings [papillary atrophy, edema, necrosis, hyperplasia of the pelvic epithelium, degeneration/regeneration of the tubular epithelium, tubulo-interstitial nephritis, and dilatation of the tubules] at the high-dose level in both sexes [both generations] and to a lesser degree in the mid-dose males [second generation]. Decreased absolute liver weight was observed in the high-dose males of both generations and in the high-dose females in the second generation, which was attributed to the nutritional status, lower body weights, and decreased abdominal fat of these rats. Reproductive indices [mating performance, fertility, gestation length, time to mating, and the pup sex ratio] of both generations were not adversely affected by exposure to Fluroxypyr up to the limit dose in females and 750 mg/kg/day in males. Pup survival [F2A 94.5% vs 98.9%/F2B 92.1% vs 99.7% high dose vs control] and consequently litter sizes were decreased slightly in the F2A and F2B litters at the high-dose level. The author attributed the decrease to a few dams with compromised heath, as evidenced by their decreased amount of body fat and moderate to severe renal disease, although this was not very apparent from the data as presented. There were no apparent effects observed on pups at the mid- or low-dose level. F1 pup body weight at the high-dose level was comparable to the control during lactation, but body-weight gain was initially [day 1-4] lower than the control [♂♂ 81%.♀♀ 88% of control]. Decreased body weight was observed throughout lactation in both the F2A [♂♂ 85%-91%/♀♀ 86%-92% of control] and F2B pups [♂♂ 86%-92%/♀♀ 89%-94% of control; P2 89-93% of control]. Decreased body-weight gain was observed throughout lactation for both the F2A and F2B pups, but the magnitude of the decrease was greatest initially [days 1-4]. Overall, body-weight gain during lactation was only slightly lower than the control for both the F2A [♂♂ 90%/♀♀ 92% of control] and F2B [♂♂ 92%/♀♀ 94% of control] pups. **The NOEL for maternal/paternal toxicity is 500/100 mg/kg/day], and the LOEL is 1000/500 mg/kg/day], based on death in females and increased kidney weight with corresponding gross and microscopic findings [papillary atrophy, edema, necrosis, hyperplasia of the pelvic epithelium, degeneration/regeneration of the tubular epithelium, tubulo-interstitial nephritis, and dilatation of the tubules] in both sexes. The reproductive NOEL is 1000/750 mg/kg/day], the highest dose tested. The neonatal NOEL is 500 mg/kg/day, and the LOEL is 1000 mg/kg/day, based on decreased pup body weight/body-weight gain and slightly lower survival.**

This guideline [§83-4; OPPTS 870.3800] 2-generation reproduction study in rats is classified 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 [Table 1, page 52]
Source: DowElanco
CAS #: 69377-81-7/81406-37-3
Empirical Formula: $C_7H_5Cl_2FN_2O_3$
STRUCTURE

2. Vehicle: none

3. Test animals: Species: rat
Strain: Sprague-Dawley
Age at start of dosing: (P1) ≈6 weeks; (P2) 3 weeks
Weight at start of dosing: (P1) Males: 104.4-132.2 g; Females: 100.6-120.7 g; (P2) Males: 124.5-195.1 g; Females: 107.4-152.2 g [2 outliers included (67.1 & 77.2 g)]
Source: Charles River Breeding Laboratory, Kingston, NY
Housing: individually [pre-mating] in wire mesh stainless steel cages; dams housed individually from ≈day 19 of gestation in plastic cages [corn-cob nesting material]
Diet: Purina Certified Rodent Chow No. 5002 ad libitum
Water: municipal drinking water ad libitum
Acclimation period (P1): ≈2 weeks

B. PROCEDURES AND STUDY DESIGN

1. Mating procedure: Each breeding period involved three 7-day cohabitation periods with one female being housed with one male from the same dose group following a 10-week P1/12-week P2 pre-mating period during which the test material was administered via the diet at dose levels of 0, 100, 500, and ♂♂ 750/♀♀ 1000 mg/kg/day. For the P2 matings, cohabitation with litter mates was avoided. Daily vaginal lavage samples were evaluated for the presence of sperm. When sperm were observed or a vaginal copulatory plug was observed in situ, each female was returned to her own cage until ≈ day 19 of gestation when they were placed into individual plastic cages provided with ground corn cob nesting material. After the first 7-day mating period, unmated females were co-housed with an alternate male of the same dose group for a second/third 7-day mating period. Females that never showed evidence of insemination after 3 cohabitation periods were placed in individual nesting cages at the end of the 3rd week of breeding.

2. Study schedule and animal assignment: Rats purchased for the study were weighed on test day -9 and ranked according to body weight using a computerized procedure. Those from the extremes of the distribution were identified and removed from the population until only the number of rats required for the study remained. These rats were randomly assigned by weight to treatment groups to increase the probability of uniform group mean weights at the start of the study. The rats were divided into 4 groups of 30/sex/group. Selection of the weanlings to become parents of the F2 generation was performed randomly [not further defined]. To reduce variation in the growth of the pups, the F1, F2a, and F2b litters with more than 8 pups were culled on lactation day 4. Culled litters were reduced to 4 pups/sex where possible using a computer-generated randomization procedure. Preferential culling of runts was not performed. Male and female rats chosen for the study were provided with test diets for ten weeks/twelve weeks prior to mating of the first parental [P1]/second parental [P2] generations, respectively. NOTE: To avoid the potential of overdosing during the breeding period, rats "cohoused were provided with the lower of the two concentrations (either male or female) for that dose group (low, middle or high). During gestation, females from each dose group were provided with the appropriate dietary concentration of fluroxypyr given during breeding." [Reviewer assumes this latter statement is in error and should read that they were provided the concentrations given during the pre-mating phase] Dietary concentrations supplied during lactation were adjusted using historical control feed consumption data for lactating females in order to maintain a constant mg/kg/day dose during this period. During the interval between weaning of the first and last litters, weanlings chosen for the P2 generation were maintained on the same diet that was given to the P1 females during the last week of lactation. Dietary concentrations for the P2 generation were calculated as described for the P1 animals."

It was stated that, due to an oversight by the technologist responsible for diet mixing/feeding, **diets were mixed from a pre-mix containing the wrong test material for a brief period during the second generation.** The maximal time that the incorrect diet was available to a given rat was five days, while the incorrect diet was available to many rats for fewer than 5 days or not at all, depending on the individual rat's feeding schedule. Additionally, it was stated that the incorrect test material to which the rats were exposed was not predicted to exert significant, if any, toxicity at the levels present in the diets, based on available toxicological data for the compound. Also, almost all of the data up to and including lactation day 4 for the F2a litters were collected before the mixing error occurred, and therefore, "remained valid". Approximately one week after weaning of the last F2a litters, the P2 adults were again mated to produce the F2b litters to compensate for the technical problem with the F2a litter. "Breeding of a second litter allowed for at least one complete litter in the second generation that was not impacted by the error in dietary preparation. A second breeding of the second generation adults also served to confirm the effects detected on pup

body weight which were observed in the F2a litter."

4. Dose selection rationale: The dose levels utilized were said to have been based on the results of a range-finding study in Sprague-Dawley rats [Schroeder, 1994; DECO-HET K-129976-011].

5. Dosage preparation and analysis

Diets were prepared weekly by serially diluting a Fluroxypyr/ feed concentrate [premix]. The homogeneity of the test material in the diets was determined during the course of the study. Test diets were analyzed at least 3 times/generation to determine the concentration of Fluroxypyr attained. The stability of Fluroxypyr in basal rodent feed was determined previously to be at least 28 days. Additionally, the stability of Fluroxypyr in the test diets was confirmed during the course of the study. The test diets were stored at room temperature.

RESULTS

Homogeneity Analysis: The diets were mixed homogeneously [Table 5, page 56 of the report].

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 rat 2-year study. In the current study, the diets were found to be stable for at least 58 days [Table 6, page 57].

Concentration Analysis: The test diets were found to contain the acceptable amounts of test material. The average concentrations of Fluroxypyr in the diets ranged from 94% to 101% of the target concentrations [Table 4, page 55].

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 1, page 52 of the report].

C. OBSERVATIONS

1. Parental animals: The rats were observed twice a day for morbidity, moribundity, mortality, changes in behavior or demeanor, or overt signs of toxicity, and thorough clinical examinations were conducted weekly on each P1 and P2 rat. All adult rats found dead were submitted for a gross pathologic examination. Any pup found dead during lactation was examined grossly to the extent possible and discarded. Body weight and food consumption of each male and female were measured once a week during the 10/12-week pre-mating periods. Body weight and food consumption of the males were recorded weekly throughout the study. Both of these parameters were monitored for the dams during gestation and lactation as follows: **body weight** days 0, 7, 14, and 21 [gestation]; days 1, 4, 7, 14, and 21 [lactation]; **food consumption**

once a week [gestation] and twice during the first and second week of lactation and at 2-3 day intervals during this phase of the study for females that failed to deliver. The same schedule was followed for the P2 generation.

2. Litter observations: Parturition was observed for signs of difficulty or unusual duration [dystocia]. The day of delivery was defined as the first day one or more pups were found and was designated as lactation day 0. Each litter was examined as soon as possible after delivery appeared to be completed, and the date of parturition, litter size [day 0], the number of live and dead pups on lactation days 0, 1, 4, 7, 14, and 21, and the sex and weight of each pup on lactation days 1, 4 [prior and after culling], 7, 14, and 21 were recorded. During lactation, any visible physical abnormalities or demeanor changes in the pups were recorded.

3. Postmortem observations

a) Parental animals: All P1 and P2 adults [fasted overnight] were subjected to a complete necropsy after the majority of litters of the respective generation were weaned. Each adult was weighed, anesthetized with methoxyflurane, and euthanized. The eyes were examined in situ by gently pressing a moistened glass slide against the cornea and observing the eyes under a fluorescent light. The liver and kidneys were weighed, and the tissues listed below were collected and preserved. Histopathological examinations were performed on the cervix, coagulating glands, epididymides, kidneys, liver, mammary gland, ovaries, oviduct, pituitary, prostate, seminal vesicles, testes, uterus, vagina, and gross lesions from all control and high-dose male and female P1 and P2 rats, where appropriate for the sex. The liver and kidneys were examined from all rats in the low- and mid-dose groups also, in light of the known kidney toxicity of the test material and to assess the appearance of the major organ associated with the metabolism of Fluroxypyr. Additionally, because of a consistent gross necropsy observation of a thickened limiting ridge in the stomachs of the high dose, the stomach was examined in the P2 females.

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/subcutis
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

b) Offspring: Pups culled on day 4 were examined grossly, euthanized with Beuthanasia-D Solution, and discarded. Any weanlings not held for the next generation or selected for necropsy were examined grossly, euthanized by CO_2 asphyxiation, and discarded. At weaning, 10 pups/sex/group from the F1, F2a, and F2b litters were randomly selected for a complete necropsy. These pups were anesthetized with methoxyflurane and euthanized by decapitation. Gross pathologic examination and preservation of tissue samples [see above] were performed as described for the adults, except that the weanlings were not fasted overnight and terminal body weights were not recorded. Also, no organ weights were recorded for the weanlings. Histologic examination of the tissues was not performed.

D. DATA ANALYSIS

1. Statistical analyses: Body weight/gains: initially evaluated by Bartlett's test for equality of variances; based on outcome, either a parametric or nonparametric analysis of variance [ANOVA] was performed. If significant, a Dunnett's test or the Wilcoxon Rank-Sum test with Bonferroni's correction was performed. Food consumption: descriptive statistics [means and standard deviation. Gestation length, average time to mating, litter size: nonparametric ANOVA. If significant, the Wilcoxon Rank-Sum test with Bonferroni's correction was performed. Statistical outliers were identified by the method of Grubbs [1969] and routinely excluded from analysis for feed consumption only. Fertility indices: Fisher exact probability test and Bonferroni's correction used for multiple testing of groups in comparison to a single control. Neonatal sex ratio: binomial distribution test. Survival indices and other incidence data among neonates: Wilcoxon test as modified by Haseman and Hoel [1974], using the litter as the experimental unit.

2. Indices

Reproductive indices: The following indices were calculated for each group.

female mating index (%) - # sperm positive or pregnant ♀♀ / # ♀♀ co-housed with ♂♂ X 100

male mating index (%) - # ♂♂ mated that resulted in sperm positive or pregnant ♀♀ / # ♂♂ co-housed with ♀♀ X 100

female conception index (%) - # ♀♀ delivering a litter / # ♀♀ mated x 100

male conception index (%) - # ♂♂ that sired a litter / # ♂♂ mated x 100

female fertility index (%) - # ♀♀ delivering a litter / # ♀♀ cohoused with ♂♂ X 100

male fertility index (%) - # ♂♂ that sired a litter / # ♂♂ cohoused with ♀♀ X 100

gestation index (%) - # ♀♀ delivering a live litter / # ♀♀ delivering a litter X 100

3. Historical control data: Reproduction data, mean fetal weight data, pre- and postimplantation loss data, malformation incidence data, ossification variation data from studies conducted at testing facility from 6/86 to 12/91 [pages 446-456 of report] were submitted.

II. **RESULTS**

A. PARENTAL ANIMALS

1. Mortality and clinical signs: Four P1 adult rats died on test. One control female died on test day 72, and death was due to lymphosarcoma. One high dose [750 mg/kg/day] male [test day 100] and two high dose [1000 mg/kg/day] females [test days 48 and 71] died on test due to renal failure, and these deaths were considered treatment-related. There were no other treatment-related effects observed. Four high-dose P2 males were noted as thin and there was an increased incidence of roughened haircoat in these males. Six P2 adults died on test {two control females [days 127 and 132], one high-dose male [day 112, renal failure], one low-dose female [day 112, dystocia], and two high-dose females [day 50 (renal failure and duodenal ulcer); day 167 (vaginal bleeding and tissue anoxia)]}. No treatment-related clinical signs were reported.

2. Body weight and food consumption: PRE-MATING **P1 Generation** - Body weight of the high-dose P1 males during the pre-mating period was slightly lower than the control [95% of control by week 10] and significantly lower from day 90 until sacrifice [91-94% of control]. Body-weight gain of the high-dose P1 males during the dosing period was slightly lower [93% over the 10-week dosing period] than the

control and by week 20 was 88% of the control value. Body weight was comparable among the P1 female groups during the 10-week dosing period, and body-weight gain during the dosing period was slightly lower [97% of control] at the high-dose level compared to the control. Food consumption was comparable among the groups of P1 males during the pre-mating period, but a slight decrease [91-93% of control] in food consumption was observed during the last few weeks on test [days 113-134]. Food consumption was comparable among the P1 females throughout the dosing period. **P2 Generation** - Body weights and body-weight gains of the low- and mid-dose male P2 rats were comparable among the groups during the pre-mating period. At the high-dose level, lower body weight was observed throughout the study, beginning pre-dose [day -2] when body weight for this group was ≈93% of the control value. Week 12 body weight at the high-dose level was 91% of the control value. Body-weight gain over the 12-week dosing period [day -2-83] was 91% of the control value. Decreased body weight was observed in the high-dose P2 females throughout the dosing period [88-94% of control], and body-weight gain during the dosing period was lower than the control also [91% of control]. Food consumption was decreased at the high-dose level in both sexes [♂♂ 92%-95%/♀♀ 93%-98% of the control] throughout the dosing period. DAMS **P1 Generation** - At the high-dose level, the dams displayed comparable body weights during gestation, although by gestation day 21 body weight was slightly less than [96% of control] the control. Body-weight gains were decreased at the high-dose level throughout gestation [84-89% of control]. On day 1 of lactation, there was a significant decrease [94% of control] in body weight at the high-dose level compared to the control, but thereafter, comparable values were observed among the groups. Body-weight gains were greater than the control for all dose groups during days 1-4 and throughout lactation at the high-dose level. Overall, there was a dose-related increase in body-weight gains, and the increase at the mid- and high-dose levels was statistically significant. Food consumption was slightly decreased [95-97% of control] during gestation compared to the control. During lactation, except for days 1 through 4, comparable food consumption was observed among the groups. During days 1-4 of lactation, food consumption of the high-dose dams was 83% of the control value. DAMS **P2 Generation [F2A litters]** - At the high-dose level, decreased body weight was observed throughout gestation [88-92% of control] and lactation [86-96% of control]. With the exception of the day 7-14 interval, body-weight gains were decreased throughout gestation. During lactation, body-weight gains were significantly increased at the high-dose level, and overall, there was a dose-related increase in body-weight gain at the mid- and high-dose levels. Food consumption was decreased throughout gestation and for most intervals during lactation. DAMS **P2 Generation [F2B litters]** - Decreased body weight was observed throughout gestation at the high-dose level [86%-91% of the control], and body-weight gains were also decreased throughout gestation [74% of control overall]. During lactation, body weight at the high-dose level was lower [86-93% of control] than the control, but during the last week of lactation, body weight for this group was nearly comparable

9

[96% of control] to that of the control. During days 1-4 of lactation, the high-dose dams gained only 2.2 grams compared to 11.8 grams in the control. Thereafter, the high-dose dams gained significantly more weight than the controls. Slightly lower food consumption was found at the high-dose level compared to the control during gestation [92%-97% of control], but with the exception of initially [days 1-4], comparable food consumption was observed among the groups during lactation.

Table 1. Body Weight [grams]/Gain [grams] During PRE-MATING

Generation/Time/Dose	0	100	500	750/1000
P1 Generation BW - males				
day -2	186.4	186.8	185.6	184.1
day 6	239.9	241.4	240.3	237.1
day 13	291.3	293.8	291.5	286.0
day 20	333.8	340.9	336.3	327.4
day 27	370.2	376.7	370.9	358.3
day 69	491.2	508.6	496.1	468.9
day 90	521.9	540.9	525.7	491.0*[94]♪
day 111	552.3	568.5	551.1	515.1*[93]
day 125	568.0	583.2	564.8	517.0*[91]
day 139	582.8	597.9	580.2	533.3*[92]
P1 Generation BW - females				
day -2	144.8	144.2	147.2	147.1
day 6	165.0	162.6	169.0	165.3
day 13	182.7	181.9	187.9	185.0
day 20	196.7	194.2	203.2	199.1
day 27	209.6	206.3	216.9	211.3
day 69	256.3	254.8	268.1	255.4
P2 Generation BW - males				
day -2	156.6	157.2	157.4	145.5[93]
day 6	214.4	218.1	214.6	199.7*[93]
day 13	277.2	279.8	276.3	258.4*[93]
day 20	333.0	335.7	330.6	310.0*[93]
day 27	373.3	373.3	369.4	346.4*[93]
day 69	518.5	521.3	513.2	477.4*[92]
day 90	538.7	551.0	536.6	495.2*[92]
day 125	590.2	605.9	595.2	537.8*[91]
day 139	605.1	623.1	612.4	540.9*[89]
day 160	609.6	626.3	619.2	549.7*[90]
P2 Generation BW - females				
day -2	128.0	126.3	128.5	121.7[95]
day 6	154.7	151.2	155.7	145.5*[94]
day 13	178.8	175.0	181.1	167.5*[94]
day 20	200.3	196.1	201.2	186.4*[93]
day 27	213.9	210.2	217.2	200.0*[94]
day 69	272.6	268.5	275.8	252.9*[93]
day 139	315.1	303.9	309.3	278.2*[88]
P1 Generation - gain♦ [day -2-69]				
males	304.8	321.8	310.5	284.8[93]
females	111.5	110.6	120.9	108.3[97]
P2 Generation - gain♦ [day -2-83]				
males	384.7	393.5	377.5	348.7[91]
females	151.7	149.8	158.3	138.5[91]

data from Tables 12, 13 [pages 64-66], Tables 36, 37 [pages 111-114] of the report; ♦ calculated

by reviewer using data from pages 64-66 and 111-114 of report; ♪ [% of control]; *α <0.05

Table 2. Body Weight [grams]/Gain [grams] of DAMS

Generation/Time/Dose	0 ppm	100	500	1000
P1 Generation - body weight				
gestation day 0	259.9	256.9	269.3	262.7
gestation day 7	290.1	288.3	299.5	289.6
gestation day 14	319.8	317.1	328.3	315.9
gestation day 21	396.7	394.9	400.8	379.6
P2 Generation [F2A] - body weight				
gestation day 0	277.5	274.8	282.4	252.6*[91]
gestation day 7	309.7	305.9	308.6	281.5*[91]
gestation day 14	334.6	334.6	336.3	308.1*[92]
gestation day 21	408.2	412.0	407.9	360.4*[88]
P2 Generation [F2B] - body weight				
gestation day 0	320.7	312.7	316.9	292.2*[91]
gestation day 7	354.4	348.2	350.9	321.5*[91]
gestation day 14	385.9	381.6	379.6	345.3*[89]
gestation day 21	466.5	460.2	457.9	400.1*[86]
P1 Generation body weight				
lactation day 1	296.2	295.0	298.2	278.3*[94]
lactation day 4	302.2	305.3	309.6	291.6[96]
lactation day 7	310.4	314.1	316.9	305.7
lactation day 14	329.9	337.3	340.4	330.8
lactation day 21	315.1	317.2	327.3*	320.3
P2 Generation [F2A] body weight				
lactation day 1	309.5	313.4	307.5	270.3*[87]
lactation day 4	317.3	319.4	317.6	272.5*[86]
lactation day 7	323.2	323.8	326.3	285.9*[88]
lactation day 14	339.1	343.2	342.6	313.3*[92]
lactation day 21	325.6	322.2	331.7	314.0[96]
P2 Generation [F2B] body weight				
lactation day 1	350.5	351.3	341.3	304.2*[87]
lactation day 4	362.2	362.5	355.2	310.2*[86]
lactation day 7	365.1	364.0	360.1	324.8*[89]
lactation day 14	381.2	379.6	377.5	353.4*[93]
lactation day 21	360.8	356.4	368.9	345.1[96]
P1 Generation gain				
gestation	136.3	139.3	131.4[96]	117.0*[86]
lactation	19.0	21.1	29.1*	42.0*
P2 Generation [F2A] gain				
gestation	130.7	137.2	125.5	107.8*[82]
lactation	13.5	8.8	24.2*	41.6*
P2 Generation [F2B] gain				
gestation	144.4	147.5	140.9	107.2*[74]
lactation	10.3	5.1	27.6*	37.1*

data from pages 64-70, 111-118, and 126-129 of report; *α <0.05

3. Reproductive function

a. Estrous cycle length and periodicity: These parameters were not monitored.

b. Sperm measures: No data on sperm parameters were provided.

c. Sexual maturation (F_1): These data were not provided.

4. Reproductive performance: There were no adverse effects on male or female mating, conception, or fertility indices, on the length of gestation, time to mating, or sex ratio in any generation, but there was a decrease in pup survival [day 0-4] in the high-dose F2B litters. Pup survival was comparable among the groups in both the F1 and F2A litters [Tables 3, 4, and 5].

Table 3. Reproductive Performance - P1 Dams

Parameter/Dose [mg/kg/day]	0	100	500	1000
# of females	29	30	30	28
female mating index [%]	100	100	100	100
female conception index [%]	89.7	100	90	92.9
female fertility index [%]	89.7	100	90	92.9
gestation index [%]	100	100	100	100
# of males	29	30	30	30
male mating index [%]	96.6	100	96.7	90.0
male conception index [%]	92.9	100	89.7	92.6
male fertility index [%]	89.7	100	86.7	83.3
gestation length [days]	21.6±0.6	21.8±0.7	21.7±0.5	21.7±0.5
time to mating [days]	3.2±1.8	2.7±1.4	2.5±1.8	4.0±3.6
pup survival indices (%)				
gestation♥	99.1 [334/337]	99.5 [374/376]	99.5 [369/371]	97.1 [325/332]
day 1♦	99.4 [332/334]	99.2 [371/374]	99.7 [368/369]	99.7 [324/325]
day 4♦	99.1 [331/334]	98.7 [369/375]	99.2 [366/369]	99.4 [323/325]
day 7♣	100 [206/206]	99.6 [231/232]	99.5 [212/213]	99.5 [205/206]
day 14♣	100 [206/206]	99.6 [231/232]	99.5♪ [212/213]	99.5 [205/206]
day 21♣	100 [206/206]	99.6 [231/232]	99.5 [212/213]	99.5 [205/206]
sex ratio on day 1 [♂:♀]	52:48	47:53	51:49	50:50

♥ % of newborn pups that were alive at birth [# alive at birth/# born]; ♦ # live pups on day 1 or 4/# live pups on day 0 x 100; ♣ # live pups on day 7, 14, or 21/# live pups on day 4 after culling x 100; ♪ incorrectly listed as 100 in report; data from Table 18 of the report [pages 71-72]

Table 4. Reproductive Performance - P2 Dams [F2A litters]				
Parameter/Dose [mg/kg/day]	0	100	500	1000
# of females	30	30	29	29
female mating index [%]	93.3	100	96.6	100
female conception index [%]	82.1	93.3	96.4	93.1
female fertility index [%]	76.7	93.3	93.1	93.1
gestation index [%]	100	100	100	100
# of males	30	30	29	29
male mating index [%]	93.3	96.7	96.6	96.6
male conception index [%]	82.1	96.6	96.4	96.4
male fertility index [%]	76.7	93.3	93.1	93.1
gestation length [days]	21.9±0.4	21.8±0.4	21.8±0.4	21.6±0.5
time to mating [days]	2.9±1.4	3.3±3.2	3.1±1.1	2.9±3.0
pup survival indices (%)				
gestation♥	98.9 [275/278]	97.1 [340/350]	96.2 [308/320]	99.3 [292/294]
day 1♦	100 [275/275]	97.4 [331/340]♪	99.4 [306/308]	96.2 [281/292]
day 4♦	98.9 [272/275]	100 [331/331]	98.1 [302/308]	94.5 [276/292]
day 7♣	100 [272/272]	100 [212/212]	100 [205/205]	99.0 [192/194]
day 14♣	100 [164/164]♠	100 [212/212]	99.5 [204/205]	99.0 [192/194]
day 21♣	100 [164/164]	100 [212/212]	99.5 [204/205]	99.0 [192/194]
sex ratio on day 1 [♂/♀]	46:54	51:49	52:48	50:50

♥ % of newborn pups that were alive at birth [# alive at birth/# born]; ♦# live pups on day 1 or 4/# live pups on day 0 x 100; ♣ # live pups on day 7, 14, or 21/# live pups on day 4 after culling x 100; ♠ change in pup # after day 7 due to pups of one dam euthanized on lactation day 13 [accidental death]; ♪ incorrectly listed as 100.0 (331/331) in report;
data from Table 42 of the report [pages 119-120]

Table 5. Reproductive Performance - P2 Dams [F2B litters]

Parameter/Dose [mg/kg/day]	0	100	500	1000
# of females	30	30	30	30
female mating index [%]	96.4	100	100	100
female conception index [%]	85.2	96.6	86.2	93.1
female fertility index [%]	82.1	96.6	86.2	93.1
gestation index [%]	100	100	100	96.3
# of males	28	29	29	28
male mating index [%]	89.3	100	93.1	96.4
male conception index [%]	88.0	96.6	88.9	92.6
male fertility index [%]	78.6	96.6	82.8	89.3
gestation length [days]	21.9±0.4	21.8±0.4	21.6±0.6	21.5±0.5
time to mating [days]	3.6±3.4	2.6±1.1	3.6±4.4	2.9±2.0
pup survival indices (%)				
gestation♥	99.1 [333/336]	97.7 [382/391]	97.2 [353/363]	95.1 [331/348]
day 1♦	100 [333/333]	99.5 [380/382]	98.9 [349/353]	93.7 [310/331]
day 4♦	99.7 [332/333]	98.2 [375/382]	98.9 [349/353]	92.1 [305/331]
day 7♣	100 [184/184]	99.5 [220/221]	99.5 [193/194]	98.9 [181/183]
day 14♣	99.5 [183/184]	99.5 [220/221]	99.5 [193/194]	98.4 [180/183]
day 21♣	99.5 [183/184]	99.5 [220/221]	99.0 [192/194]	98.4 [180/183]
sex ratio on day 1 [♂/♀]	50:50	51:49	52:48	51:49

♥ % of newborn pups that were alive at birth [# alive at birth/# born]; ♦# live pups on day 1 or 4/# live pups on day 0 x 100; ♣ # live pups on day 7, 14, or 21/# live pups on day 4 after culling x 100; data from Table 52 of the report [pages 130-131]

4. Parental postmortem results

a) Organ weights: Only the kidneys and liver were weighed. Males at the high-dose level of both generations displayed slightly lower [91-94% of the control] liver weights compared to the controls. The high-dose P2 females displayed a lower [89% of control] absolute liver weight than the control. The kidney is the major target organ of Fluroxypyr, and an increase in absolute kidney weight was observed in the high-dose P1 males, the low- and mid-dose P2 males, the mid- and high-dose P1 females, and the high-dose P2 females [Table 6]. Increased relative kidney weights were displayed in P1 males at the mid- and high-dose levels, in P2 males at all dose levels, and in P1 and P2 females at the high-dose level.

15

Table 6. Organ Weights

Dose [mg/kg/day] Generation Organ	MALES		FEMALES	
	P1 generation	P2 generation	P1 generation	P2 generation
KIDNEY				
absolute				
0	3.609	3.735	2.093	2.444
100	3.713	4.132* [111]	2.101	2.523
500	3.825	4.142* [111]	2.233* [107]	2.577
750/1000	4.040* [107]	3.955 [106]	2.295* [110]	2.623* [107]
relative				
0	0.657	0.642	0.747	0.801
100	0.658	0.689* [107]	0.755	0.842
500	0.701* [107]	0.699* [109]	0.773	0.839
750/1000	0.814* [124]	0.766* [119]	0.821* [110]	0.964* [120]
LIVER				
absolute				
0	14.269	15.574	7.729	10.080
100	15.133	16.534	7.736	9.865
500	14.813	16.575	8.128	10.067
750/1000	13.407 [94]	14.112 [91]	7.827	8.933* [89]
relative				
0 ppm	2.587	2.669	2.754	3.299
20 ppm	2.673	2.743	2.776	3.289
100 ppm	2.697	2.786	2.811	3.271
500 ppm	2.658	2.685	2.794	3.279
TERMINAL BW [g]				
0	550.5	583.1	280.3	306.7
100	566.3	600.0	278.8	300.1
500	549.2	593.6	288.9	308.9
750/1000	502.2* [91]♦	525.4* [90]	280.2	272.9* [89]

* $\alpha<0.05$; ♦ (% of control); data from Tables 22, 23, 56, 57 [pages 76, 77, 135, 136] of the report

b) Pathology

1) Macroscopic examination: There were no treatment-related findings reported for any tissue/organ except the kidney. Effects in the kidney attributed to treatment at the high dose were decreased or increased size; mottled; focus - pale, cortex; and roughened surface. Another treatment-related finding was a decreased amount of fat in the abdominal cavity, which correlated with the decreased body weight at the high-dose level for both sexes [P1: ♂♂ 13%, 10%, 17%, 57%/♀♀ 10%, 7%, 3%, 27%; P2: ♂♂ 17%, 13%, 3%, 47%; ♀♀ 23%, 10%, 20%, 87% in control, low-, mid-, and high-dose adults; pages 84 & 146 of report]. No gross findings were observed at the low- and mid-dose levels in either sex of the P1 generation. In the P2 females at the high dose [24/30 vs 0/30], a slight increase in the thickness of the limiting ridge of the stomach was observed, which was attributed to decreased food consumption, decreased body weight, and was accentuated by the stress of pregnancy and lactation.

2) Microscopic examination: In the rats dying on test, kidney toxicity [variable degree of papillary atrophy with or without necrosis, hyperplasia of the pelvic epithelium, degeneration of the tubules, tubulointerstitial nephritis, and dilatation of the tubules with or without cellular debris] was evident. Similar changes were observed in survivors [Table 7].

16

Table 7. Histopathology Observations

Organ/Dose [mg/kg/day] Generation Sex [n=30/sex]	P1 generation adults♪		P2 generation adults♬	
	males	females	males	females
KIDNEY				
papillary atrophy				
0	1	0	0	0
100	0	0	0	0
500	0	0	3	0
750/1000	8	5	21	13
hyperplasia, pelvic epithelium				
0	2	3	3	2
100	0	0	2	0
500	1	0	3	1
750/1000	5	5	19	19
degeneration of tubules				
0	27	9	27	18
100	25	5	27	12
500	23	8	27	14
750/1000	23	27	29	29
tubulointerstitial nephritis				
0	0	0	0	0
100	0	0	0	0
500	0	0	2	0
750/1000	7	1	8	6
dilatation of tubules				
0	0	0	0	1
100	0	0	0	0
500	0	0	3	0
750/1000	8	3	17	12
papillary necrosis				
0	0	0	0	1
100	0	0	0	0
500	0	0	0	0
750/1000	2	1	4	4
edema, papilla(e)				
0	0	0	0	0
100	0	0	0	0
500	2	0	0	0
750/1000	0	3	1	0
papillary cysts				
0	-	-	0	0
100	-	-	0	0
500	-	-	2	0
750/1000	-	-	15	5
LIVER				
atrophic appearance				
0	0	1	0	0
100	0	0	0	0
500	2	0	0	0
750/1000	4	2	3	1
STOMACH				
thickened, limiting ridge				
0	-	-	-	1
100	-	-	-	0
500	-	-	-	1
750/1000	-	-	-	27

♦ n=30 all groups; ♬ n=30 all groups except mid-dose ♀♀ [n=29]; - not observed
data from Tables 30 and 65 [pages 98-104 and 164-171

18

B. OFFSPRING

1. Viability and clinical signs: **F1 Litters** - One runt was observed in both the mid- and high dose groups, and there were 2 malformed pups [both dead, 2 litters; anophthalmia-bilateral, mandibular proboscis with whiskers present in one and agnathia and aglossia in another] at the high-dose level [332 pups at birth, 325 alive]. There were no treatment-related clinical signs observed. **F2A Litters** - One malformed pup [exencephaly, ablepharia, and macroglossia] was observed at the high-dose level. There were no treatment-related clinical signs observed. **F2B Litters** - One runt was observed in the control. Seven high-dose fetuses were dehydrated. One high-dose litter had only dead fetuses [11]. There were no treatment-related clinical signs observed.

2. Litter size: **F1 Litters**: Litter size was comparable among the groups at birth and throughout lactation [Table 8]. There was no adverse effect on survival at any dose level. **F2A Litters**: At birth, the high-dose litter size was smaller [90% of control] than the control and remained slightly lower throughout lactation due to the fact that there were not enough pups available on day 4 pre-cull from which to choose to equalize litter size to 8 pups/litter/group. Litter size at the low- and mid-dose levels was unaffected be treatment. Survival was comparable among the groups [Table 9]. **F2B Litters**: Litter size was decreased at the high-dose level at birth [88% of control] and on day 1 [82% of control]. Although the author stated that litter size at the high dose remained lower than control throughout lactation, the litter that had only dead fetuses at birth was used in the calculations throughout the study, which is not appropriate. When this litter and that of two other litters with no pups after day 1 are eliminated from the calculations, litter size at the high dose from day 4 post-cull to day 21 was comparable to the control. Litter size was comparable to the control at the low- and mid-dose levels. There was no treatment-related effect on survival [Table 10].

Table 8. F1 Pup Viability and Litter Size

Parameter/Dose [mg/kg/day]	0	100	500	1000
# fetuses at birth♥ # alive♥ # per litter # dead/# dams w/dead fetuses♥	337 334 12.8 3/2	376 374 12.5 2/2	371 369 13.7 2/2	332 325 12.5 7/6
live count-day 1 [#♥/litter]	332 [12.8]	371 [12.4]	368 [13.6]	324 [12.5]
live count-day 4♪ [#♥/litter]	331 [12.7]	369 [12.3]	366 [13.6]	323 [12.4]
live count-day 4♦ [#♥/litter]	207 [7.96]	232 [7.7]	213 [7.9]	206 [7.9]
live count-day 7 [#♥/litter]	206 [7.9]	231 [7.7]	212 [7.9]	205 [7.9]
live count-day 14 [#♥/litter]	206 [7.9]	231 [7.7]	212 [7.9]	205 [7.9]

19

live count-day 21 [#♥/litter]	206 [7.9]	231 [7.7]	212 [7.9]	205 [7.9]

data from Tables 19 and A-16 [pages 73, 256-259] of the report; ♥ calculated by reviewer; ♪ pre-cull; ♦ post-cull

Table 9. F2A Pup Viability and Litter Size

Parameter/Dose [mg/kg/day]	0	100	500	1000
# fetuses at birth♣ # alive♣ # per litter # dead/# dams w/dead fetuses♣	278 275 12.0 3/3	350 340 12.1 10/7	320 308 11.4 12/7	294 292 10.8 (90)♥ 2/2
live count-day 1 [#♣/litter]	275 [12.0]	331 [12.3]	306 [11.3]	281 [10.4]
live count-day 4 [#♣/litter]	272 [11.8]	331 [12.3]	302 [11.2]	276 [10.2] {10.6}
live count-day 4♦ [#♣/litter]	172 [7.5]	331 [12.3]	205 [7.6]	194 [7.1] {7.4}
live count-day 7 [#♣/litter]	172 [7.5]	212 [7.9]	205 [7.6]	192 [7.1] {7.38}
live count-day 14 [#♣/litter]	164♪ [7.5]	212 [7.9]	204 [7.6]	192 [7.1] {7.38}
live count-day 21 [#♣/litter]	164 [7.4]	212 [7.9]	204 [7.6]	192 [7.1] {7.38}

♦ post-cull; ♪ pups euthanized due to death of dam or missing data; ♥ (% of control); {mean leaving out litter with no pups after day 1}; ♣ calculated by reviewer; data from Tables 42 and A-36 [pages 120, 393-396] of the report

Table 10. F2B Pup Viability and Litter Size

Parameter/Dose [mg/kg/day]	0	100	500	1000
# fetuses at birth♣ # alive♣ # per litter # dead/# dams w/dead fetuses♣	336 333 14.5 3/3	391 382 13.6 9/4	363 353 14.1 10/5	348 331 12.7 (88)♪♠ 17/5♠
live count-day 1 [#♣/litter]	333 [14.5]	380 [13.6]	349 [14.0]	310 [11.9] (82)
live count-day 4 [#♣/litter]	332 [14.4]	375 [13.4]	349 [14.0]	305 [11.7] (81) {12.2 (85)}♫
live count-day 4♦ [#♣/litter]	184 [8.0]	221 [7.9]	194 [7.8]	183 [7.0] {7.96}
live count-day 7 [#♣/litter]	184 [8.0]	220 [7.9]	193 [7.7]	181 [7.0] {7.9}
live count-day 14 [#♣/litter]	183 [8.0]	220 [7.9]	193 [7.7]	180 [6.9] {7.8}
live count-day 21 [#♣/litter]	183 [8.0]	220 [7.9]	192 [7.7]	180 [6.9] (86) {7.8}

♦ post-cull; ♠ one litter with only dead [11] pups [excluding this litter, mean is 13.2]; ♫ excluding litter with only dead fetuses at birth {mean (% of control)}; ♪ (% of control); ♣ calculated by reviewer; data from Tables 53 and A-48 [pages 132 and 469-472] of the report

3. Body weight: **F1 Pups**: There were no adverse effects on body

20

weight in the F1 pups [Table 11]. After the first 4 days of lactation when there was a decrease in body-weight gain in both male [81% of control] and female [88% of control] pups at the high-dose level compared to the controls, body-weight gains were comparable among the groups. **F2A Pups**: Both body weight and body-weight gain were decreased in both sexes at the high-dose level compared to the controls [Table 12]. **F2B Pups**: Similar decreases to those observed in the F2A pups were observed in this second litter of pups with regard to body weight and body-weight gains at the high dose level in both sexes [Table 13].

21

Table 11. Pup Body Weight [g]/Gain [g]

Generation Day/Interval Dose [mg/kg/day]	F1 Pups							
	0		100		500		1000	
	males	females	males	females	males	females	males	females
Day 1	6.8	6.4	7.0	6.6	6.6	6.2	6.6	6.2
Day 4♦	9.5	9.0	9.8	9.3	9.3	8.9	8.8	8.5
Day 7♥	15.6	14.9	15.8	15.0	15.3	14.6	14.7	14.2
Day 14	32.4	31.0	32.7	31.4	32.5	31.5	32.3	31.3
Day 21	52.9	50.6	53.7	51.4	53.0	50.7	52.5	50.9
day 1-4♣	2.7	2.6	2.8	2.7	2.7	2.7	2.2 [81]♪	2.3 [88]
day 4-7♣	6.1	5.9	6.0	5.7	6.0	5.7	5.9	5.7
day 7-14♣	16.8	16.1	16.9	16.4	17.2	16.9	17.6	17.1
day 14-21♣	20.5	19.6	21.0	20.0	20.5	19.2	20.2	19.6
day 0-21♣	46.1	44.2	46.7	44.8	46.4	44.5	45.9	44.7

♦ pre-cull; ♥ post-cull; ♪ [% of control]; ♣ calculated by reviewer using data from page 74 of the report

Table 12. Pup Body Weight [g]/Gain [g]

Generation Day/Interval Dose [mg/kg/day]	F2A Pups							
	0		100		500		1000	
	males	females	males	females	males	females	males	females
Day 1	6.9	6.6	6.8	6.5	7.1	6.8	6.3* [91]♪	6.1 [92]
Day 4♦	9.7	9.3	9.9	9.5	10.1	9.6	8.5* [88]	8.3* [89]
Day 7♥	15.4	14.8	15.5	14.9	16.0	15.2	13.1* [85]	12.7* [86]
Day 14	31.8	30.9	31.6	30.4	32.3	30.9	29.1* [92]	28.3* [92]
Day 21	51.6	50.1	50.8	48.7	51.8	49.8	46.7 [91]	46.0* [92]
day 1-4♣	2.8	2.7	3.1	3.0	3.0	2.8	2.2[79]	2.2[81]
day 4-7♣	5.7	5.5	5.6	5.4	5.1[89]	5.6	4.6[81]	4.4[80]
day 7-14♣	16.4	16.1	16.1	15.5	16.3	15.7	16.0	15.6
day 14-21♣	19.8	19.2	19.2	18.3	19.5	18.9	17.6[89]	17.7[92]
day 0-21	44.7	43.5	44.0	42.2	44.7	43.0	40.4[90]	39.9[92]

♦ pre-cull; ♥ post-cull; ♣ calculated by reviewer using data from page 122 of the report; ♪ [% of control];

Table 13. Pup Body Weight [g]/Gain [g]

Generation Day/Interval Dose [mg/kg/day]	F2B Pups							
	0		100		500		1000	
	males	females	males	females	males	females	males	females
Day 1	6.8	6.4	7.1	6.6	6.5	6.2	6.2*[91]♪	5.8*[91]
Day 4♦	9.5	9.0	10.1	9.5	9.1	8.8	8.4*[88]	8.0*[89]
Day 7♥	15.8	14.8	16.5	15.5	15.1	14.3	13.6*[86]	13.1*[89]
Day 14	33.1	31.8	33.5	32.0	32.3	30.9	30.7*[93]	29.6[93]
Day 21	53.4	50.6	54.3	51.2	51.7	49.4	49.3*[92]	47.5[94]
day 1-4♣	2.7	2.6	3.0	2.9	2.6	2.6	2.2[81]	2.2[85]
day 4-7♣	6.3	5.8	6.4	6.0	6.0	5.5	5.2[83]	5.1[88]
day 7-14♣	17.3	17.0	17.0	16.5	17.2	16.6	17.1	16.5
day 14-21♣	20.3	18.8	20.8	19.2	19.4	18.5	18.6[92]	17.9[95]
day 0-21	46.6	44.2	47.2	44.6	45.2	43.2	43.1[92]	41.7[94]

♦pre-cull; ♥ post-cull; *α<0.05; ♣ calculated by reviewer using data from page 133 of the report;

♪ [% of control]

3. Offspring postmortem results

a) Organ weights: Organ weights were not measured for pups in either generation.

b) Pathology

1) Macroscopic examination: There were no treatment-related findings reported. A dilated pelvis involving one or both kidneys was the only finding reported and it was noted that this is a common finding in Sprague-Dawley rats at any age [Table 14].

Table 14. Macroscopic Findings in Offspring

Generation Sex Dose [mg/kg/day]	MALES				FEMALES			
	0	100	500	750	0	100	500	1000
F1 weanlings n=10								
dilated pelvis, right	0	1	1	1	0	0	1	0
dilated pelvis, left	1	0	1	1	1	0	0	0
dilated pelvis, bilateral	1	0	2	1	5	1	1	2
dilated pelvis, any symmetry	2	1	4	3	6	1	2	2
F2A weanlings n=10								
dilated pelvis, right	1	0	0	0	1	1	1	1
dilated pelvis, left	0	0	0	0	1	0	0	1
dilated pelvis, bilateral	0	1	0	0	0	1	0	2
dilated pelvis, any symmetry	1	1	0	0	2	2	1	4
F2B weanlings n=10								
dilated pelvis, right	2	1	1	1	2	0	3	0
dilated pelvis, left	2	0	1	0	0	0	1	1
dilated pelvis, bilateral	1	0	0	1	3	2	0	2
dilated pelvis, any symmetry	5	1	2	2	5	2	4	3

data from Tables 27, 61, and 62 [pages 87, 151, and 152] of the report

2) Microscopic examination: No microscopic examinations were performed on pups from either generation.

III. DISCUSSION: Sprague-Dawley rats [≈6 weeks old] of both sexes were exposed to Fluroxypyr via the diet at dose levels of 0, 100, 500, and 750/1000 mg/kg/day during the pre-mating period of 10 weeks [P1 rats]/12 weeks [P2 rats] through gestation and lactation. There was one mating of the P1 rats and two matings of the P2 rats. Treatment-related deaths occurred at the high-dose level in both generations [one P1 male, two P1 females, one P2 male, and one P2 female due to renal failure]. Decreased food consumption and body weights were observed in males at the high dose and to a lesser degree in the high-dose females. The effects observed increased progressively with time of exposure. There were increases in kidney weight with corresponding gross and microscopic findings [papillary atrophy, edema, necrosis, hyperplasia of the pelvic epithelium, degeneration/regeneration of the tubular epithelium, tubulo-interstitial nephritis, and dilatation of the tubules] at the high-dose level in both sexes

[both generations] and to a lesser degree in the mid-dose males [second generation]. Decreased absolute liver weight was observed in the high-dose males of both generations and in the high-dose females in the second generation, which were attributed to the nutritional status, lower body weights, and decreased abdominal fat of these rats. Reproductive indices [mating performance, fertility, gestation length, time to mating, and the pup sex ratio] of both generations were not adversely affected by exposure to Fluroxypyr up to the limit dose in females and 750 mg/kg/day in males. Pup survival during days 1 to 4 of lactation and consequently litter sizes were decreased slightly in the F2A and F2B litters at the high-dose level. The author attributed the decrease to a few dams with compromised heath, as evidenced by their decreased amount of body fat and moderate to severe renal disease, although this was not very apparent from the data as presented. Decreased pup body weight and body-weight gain were observed in both sexes of F2a and F2B litters, but the magnitude of the deficits was greatest initially. There were no apparent effects observed on F1, F2A, and F2B pups at either the mid- or low-dose level.

IV STUDY DEFICIENCIES: None that would adversely affect study interpretation. On page 18 of the report, the CAS No. for Fluroxypyr is listed as 81406-37-3, which is the CAS No. listed on the Material Safety Data Sheet for Fluroxypyr, 1-methylheptyl ester in MRID 44094901 [rat developmental toxicity study]. The metabolism study, the mouse carcinogenicity study, and the 90-day rat study all list 69377-81-7 as the CAS No. for Fluroxypyr. NOTE: For the record, the Registrant should reconcile these differences.

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RDI:MMorrow:8/27/97:ToxTeam: / /97

24

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

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