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EPA Reviewer: Linda L. Taylor, Ph.D.
Review Section II, Toxicology Branch II (7509C)
EPA Secondary Reviewer: K. Clark Swentzel
Review Section II, Toxicology Branch II (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Carcinogenicity [feeding]-mouse OPPTS 870.3200 [§83-2 (b)]

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

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

TEST MATERIAL (PURITY): Fluroxypyr [98.92%]

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

CITATION: Cosse, P.F., Crissman, J.W., Markham, D.A., and Corley, R.A. (1993) Fluroxypyr: 18-Month Dietary Oncogenicity Study in CD-1® Mice. The Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical Company. Laboratory Project Study ID K-129976-004, dates of experimental work [January 17, 1990 - July 17, 1991]. MRID 44080317. Unpublished.

SPONSOR: DowElanco

EXECUTIVE SUMMARY: In the carcinogenicity study in mice [MRID 44080317], Fluroxypyr [98.92% a.i.] was administered to 60 CD-1 mice/sex/dose via the diet at dose levels of 0, 100, 300, and 1000 mg/kg/day for 18 months.

There were no adverse effects on survival or clinical signs in either sex. A slight decrease in body weight was observed in the high-dose males [93% of control value at study termination] and decreased body-weight gains [overall gain ♂♂ 80%/♀♀ 92% of control] were observed at the high-dose level in both sexes. Food consumption was not adversely affected by treatment. There were no adverse effects observed on any of the monitored hematology or ophthalmoscopy parameters in either sex. At the terminal sacrifice, here was a slight increase in the incidence of distended gall bladder [both macroscopically and microscopically] in both sexes at the high-dose level and a slight increase in the number of mice of both sexes with kidneys that were considered decreased in size. Organ weights, including the kidneys, were comparable among the groups in both sexes. Microscopically, there was a significant increase in the incidence of renal papillary necrosis and regenerative nephrosis [severe grade only] in the high-dose females.

There was no apparent treatment-related increase in the incidence of any tumor type in either sex.

The LOEL is 1000 mg/kg/day, based on decreased body weight/gain in males and an increased incidence of kidney lesions in females. The NOEL is 300 mg/kg/day.

1/17

This guideline [§83-2] carcinogenicity study in the mouse is Acceptable.

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

I. MATERIALS AND METHODS

A. MATERIALS

1. Test Material: Fluroxypyr
Description: white crystalline solid
Lot #: AGR# 279095
Purity: 98.9% a.i.
Stability of Compound: stable [98.5%, 98.8% & 98.8% at 6, 12, & 18 months, respectively]
CAS #: 69377-81-7
STRUCTURE

2. Vehicle: basal diet

3. Test animals
Species: mouse
Strain: CD-1
Age at study initiation: ≈5 weeks at purchase
Weight at study initiation: ♂♂ ≈28 g/♀♀ ≈23 g on day -2
Source: Charles River Breeding Laboratory, Kingston, NY
Housing: individual stainless steel cage
Diet: Purina Certified Chow #5002, Purina Mills Co. St. Louis, MO ad libitum
Water: tap water ad libitum
Environmental conditions: normal laboratory conditions
Acclimation period: 7 days

B. STUDY DESIGN

1. In life dates - start: January 17, 1990; end: July 17, 1991

2. Animal assignment - Mice [60/sex/group] were assigned [computer-generated randomization scheme based on body weight] to 1 of 4 test groups and feed diets formulated to provide doses of 0, 100, 300, or 1000 mg Fluroxypyr/kg body weight/day for 18 months. NOTE: Due to the high mortality prior to the scheduled 12-month interim sacrifice, the 10 mice/sex/group assigned to the interim necropsy were not sacrificed to ensure an adequate number of survivors at study termination.

3. Dose Selection: Several previous toxicity studies on Fluroxypyr were described. Doses of 320 mg/kg/day resulted in no treatment-related effects following both a 13-week and a 78-week exposure period. In a 4-week range-finding study using doses up to 2000 mg/kg/day, histologic lesions in the kidneys [tubular degeneration] were observed in males at 500 mg/kg/day and above and in females at 2000 mg/kg/day. The NOEL in the study was 200 mg/kg/day. Two Japanese studies were described in which the NOEL in a 4-week study was 16 mg/kg/day for CD-1 male mice and 1540 mg/kg/day for females, and the NOEL in a subchronic study was 1500 mg/kg/day in both sexes. The limit dose was chosen as the high dose, and it was stated that renal tubular

degeneration was expected to result at this dose level. The remaining dose levels of 300 mg/kg/day and 100 mg/kg/day were chosen to assess possible dose-response relationships and a NOEL.

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. 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 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 rodent chow was established to be at least 30 days in a previous study, and the mixing method was found to be adequate. Test diets were analyzed during months 1, 4, 7, 10, 13, 16, and 18 to determine the concentration of the test material achieved.

Results

Homogeneity Analysis: The diets were found to be mixed homogeneously [previous study referenced; 96% of target].

Stability Analysis: Fluroxypyr was stable at a target concentration of 5% for 35 days and at a target concentration of 0.156% for 18 days. Diet preparations were used within a 2-week period.

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 98.9%. Analysis at ≈6-, 12-, and 18-month intervals found the purity to range from 98.5% to 98.8%.

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

6. Statistics - Body weights, organ weights, 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 comparisons. Feed consumption and white blood cell differential counts: Descriptive statistics only [means and standard deviations]. Feed efficiency: Descriptive statistics [means only]. Statistical outliers were identified by a sequential test [Grubbs], but routinely excluded only from feed consumption statistics. Histopathologic observations: [for tissues scheduled for examination from all mice] 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 mice.

C. METHODS

1. Observations

Mice 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 mouse 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 measured for each mouse once a week for the first 13 weeks and at least every four weeks thereafter. Feed efficiency was calculated for the first 13 weeks.

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

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

4. Ophthalmoscopic examinations: Ophthalmological examinations were conducted on all mice prior to study initiation and on all surviving mice at the scheduled 18-month necropsy.

5. Clinical Pathology

At 18 months, blood was collected from the first 20 surviving mice/sex/dose for clinical pathology assessment. Blood was obtained via the orbital sinus of mice anesthetized with methoxyflurane [nonfasted]. Blood samples were treated with anticoagulant, EDTA, and blood smears were prepared and stained with Wright's stain. Blood smears of the last surviving 10 mice/sex/dose, scheduled for the 12-month sacrifice, were made but not examined. 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		
	(Thromboplastin time)		
	(Clotting time)		
	(Prothrombin time)		

b. Clinical Chemistry [not examined]

6. Urinalysis [not examined]

7. Sacrifice and Pathology

All mice that died and those sacrificed on schedule [at 18 months] were subjected to a gross pathological examination, and the CHECKED (X) tissues were collected for histological examination. The brain, heart, kidneys, liver, adrenal glands, and testes were weighed. At the terminal sacrifice, microscopic examinations were performed on all collected tissues from all mice of the control and high dose levels and all mice that died or were sacrificed in a moribund condition during the study [except auditory sebaceous gland and bone joint]. Additionally, the liver, kidneys, lungs, the female reproductive tract, and any gross lesions were examined microscopically in the low- and mid-dose mice.

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
X	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 - There were no apparent treatment-related signs of toxicity observed in either sex.

2. Mortality - There was no apparent adverse effect on survival in either sex. The females had a better survival rate than the males. The most common cause of death in both sexes was systemic amyloidosis. Prior to the proposed interim sacrifice at one year, an increase in mortality of the low-dose males [27%] and the high-dose females [17%] was noted and the interim sacrifice was not performed. The first death occurred prior to the second month in both the mid- and high-dose mice of both sexes.

Table 1. Mortality [# deaths/# mice in group (%)]

Sex/Dose	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
MALES day of first death	29/60 (48) {45}♪ 142 [192]♬	35/60 (58) {68} 139 [189]	37/60 (62) {54} 34 [129]	34/60 (57) {44} 36 [167]
FEMALES day of first death	23/60 (38) {65} 209 [231]	18/60 (30) {61} 309 [335]	14/60 (23) {50} 28 [321]	26/60 (43) {50} 51 [58]

♪ {% of deaths due to systemic amyloidosis}; ♬ first [second] death; data from Tables 6, 7, 8, 9 [pages 49-60 of the report]

B. Body weight - MALES: Body weights [Table 2] of the high-dose males were decreased throughout most of the study compared to the control males, but the differences were small [96-98% of control for most of the study]. At termination, the high-dose male body weight was 93% of the control value. Body-weight gains [Table 3] fluctuated throughout the study at the high dose, with gains sometimes greater than those of the controls. Overall, the high-dose males gained less weight than the control [80% of control] and other treatment groups and during the first 90-day period, the gain was 79% of the control value. TB II notes that a lower body-weight gain [86% 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 study [Table 2]. Overall body-weight gain was slightly lower [92% of control] than the controls in the females at the high-dose level [Table 3].

Table 2. Body Weight [% of control]

Day/Sex/Dose	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
MALES			
pre-test -9	100	100	100
pre-test -2	101	100	99
6	101	99	97*
13	100	98	96*
20	101	99	96*
27	101	99	98
41	100	99	96*
62	101	99	97*
69	101	99	97*
83	101	99	97*
314	102	100	97
342	101	99	95*
370	102	100	98
510	100	100	94*
538	100	100	93*
FEMALES			
pre-test -9	100	100	100
pre-test -2	101	101	101
6	99	100	99
13	98	99	100
20	99	99	99
27	98	98	100
69	97	96*	98
76	99	98	99
83	98	96*	98
231	99	99	101
538	98	99	97

* $p<0.05$; data from Tables 16-17, pages 147-152 of the report

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Table 3. Body-Weight Gain♫ [grams (% of control)]

Interval⁋/Sex/Dose	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	1000 mg/kg/day
MALES				
pre-test	2.9	3.2	3.0	2.5 [86]♪
-2-6	2.4	2.4	2.0	1.8 [75]
6-13	1.9	1.7	1.7	1.7 [89]
13-20	1.2	1.3	1.4	1.1
20-27	0.7	0.9	0.8	1.3 [186]
27-34	0.6	0.4	0.8	0.2 [33]
34-41	0.8	0.7	0.6	0.6
41-48	0.2	0.6	0.4	0.6
83-90	-0.1	0.1	0.3	0.5
118-146	0	0.1	0.7	0.4
342-370	-0.5	0	-0.2	0.4
482-510	1.0	0.7	0.5	0.1
510-538	-0.4	-0.3	-0.2	-0.9
-2-90	9.5	9.9	9.3	7.5 [79]
-2-538	12.8	12.4	12.7	10.2 [80]
6-538	10.4	10.0	10.7	8.4 [81]
FEMALES				
pre-test	2.0	1.9	1.9	1.8
-2-6	2.4	1.8	2.0	2.0
6-13	0.6	0.5	0.5	0.7
13-20	0.9	1.0	0.9	0.8
6-55	3.9	3.6	3.5	3.9
-2-90	8.0	7.4	7.4	7.3 [91]
510-538	0.4	0.2	0.0	-0.2
-2-538	15.0	14.1	14.3	13.8 [92]
6-538	12.6	12.3	12.3	11.8 [94]

⁋ days; ♪ [% of control]; ♫ calculated by reviewer using data from Tables 16-17 [pages 147-152] of report

C. Food consumption/efficiency - There were no apparent effects in either sex on food consumption or food efficiency. The control mice of both sexes ate more feed during the pre-test period and throughout most of the study compared to all dose groups.

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

E. Hematology - There were no apparent effects observed on any of the parameters measured at 18 months, but there were no other time points monitored for comparison. There was a slight decrease [dose-related] in platelet counts in males [Table 4].

Table 4. Hematology Findings [18 months]

Parameter/dose [mg/kg/day]/sex	MALES	FEMALES
Platelet counts [$x10^3/m^3$]		
0	1678	1371
100	1664	1303
300	1610	1287
1000	1555 [93]♪	1402

♪ [% of control]; data from Tables 22 and 23, pages 161 and 163 of the report

F. Urinalysis - not performed.

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G. Sacrifice and Pathology - At the terminal sacrifice, both sexes at the high dose displayed slight, non-significant, decreases [♂♂ 95%/♀♀ 97% of control] in body weight compared to the control values.

1. Organ weight - Organ weights were comparable among the groups in both sexes, and no apparent treatment-related effects on organ weight were observed.

2. Gross pathology - There was a slight increase in the incidence of distended gall bladder in both sexes at the high-dose level [Table 5], although the author discussed only the increase in the females. It was stated that gall bladder distention is the result of bile retention, generally because of lack of digestive demand for bile in the terminally anorexic animal. According to the author, the higher incidence of this incidental, secondary finding was probably the result of variable recording by various pathologists involved in necropsy examination of dead/moribund animals, since there was no increase in dead or moribund mice in the high dose compared to the control, and most such mice were anorexic. TB II notes that all but one of these mice with distended gall bladder [both sexes] was either moribund or a spontaneous death. There was a slight increase in the number of high-dose mice of both sexes with kidneys that were noted to be decreased in size [unilateral]. The combined finding "decreased size" [symmetry recorded as left, right, unilateral, bilateral] shows an increase in both sexes at the high-dose level compared to the controls.

Table 5. Gross Pathology Findings [18 months]

Finding/dose [mg/kg/day]/sex	MALES	FEMALES
Distended gall bladder		
0	2/60 [3.3]♪	1/60 [1.7]
100	3/60 [5.0]	0/60
300	1/60 [1.7]	2/60 [3.3]
1000	5/60 [8.3]	6/60 [10]
Kidney - decreased size, unilateral		
0	1/60	0/60
100	0/60	1/60
300	0/60	1/60
1000	4/60	5/60
Kidney - decreased size [%] total		
0	1.7	1.7
100	0	1.7
300	1.7	5.0
1000	6.7	8.3

♪ [%]; data from Table 26, pages 176 and 178 of the report

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

a) Non-neoplastic - **KIDNEY** There was a significant increase [Table 6] in the incidence of renal papillary necrosis and regenerative nephrosis [severe grade only] in the high-dose females. **GALL BLADDER** The high-dose mice of both sexes displayed a higher incidence of

distended gall bladder than the control mice, as was noted grossly.

ALL OTHER ORGANS/TISSUES The control mice of both sexes displayed a higher incidence of several lesions than the treated mice. These included adrenal hyperplasia [both sexes], mediastinal and mesenteric lymph node hyperplasia [males], reactive hyperplasia in the spleen [males], erosion of the glandular mucosa of the stomach [males], and chronic inflammation of the lungs [females].

Table 6. Microscopic Observations - Non-neoplastic [all mice]

Lesion/Sex/Dose [mg/kg/day]	0	100	300	1000
MALES				
KIDNEY n=60				
necrosis, papilla(e):				
unilateral	3	3	1	5
bilateral	0	2	6	3
any symmetry	3	5	7	8
nephrosis - chronic [regenerative]:				
very slight	3	7	10	2
slight	6	1	1	3
moderate	3	4	7	7
severe	1	1	3	5
very severe	0	0	0	0
any severity	13	13	21	17
inflammation - chronic, any severity	7	1*	1*	8
FEMALES				
KIDNEY n=60				
necrosis, papilla(e):				
unilateral	3	2	3	8
bilateral	0	3	0	4
any symmetry	3 [5]♦	5 [8]	3 [5]	12* [20]
nephrosis - chronic [regenerative]:				
very slight	7	8	2	7
slight	11	5	5	5
moderate	7	3	3	6
severe	1 [1.7]	1 [1.7]	4 [6.7]	7* [11.7]
very severe	1	1	1	0
any severity	27	18	15	25
nephritis, tubulo-interstitial, slight	1	7*	9*	2
MALES				
GALL BLADDER n=	59	60	60	59
distended	2	3	1	6
FEMALES				
GALL BLADDER n=	60	60	60	59
distended	2	1	2	6

♦ [%]; * α<0.05 [Yate's Chi-square pairwise test]; data from pages 209, 220, 223-226 of report

b) Neoplastic lesions: Both sexes at the high-dose level displayed a slight increase in the incidence of adenoma in the lacrimal/Harderian gland compared to their respective control [Table 7], and there was a dose-related, slight, increase in the incidence of histiocytic sarcoma [malignant; at any site] in females. Squamous cell carcinoma [malignant] of the mammary gland was observed in one high-dose female compared with none in the concurrent control and other dose levels, and carcinoma of the pituitary was observed in one high-dose female compared to none in the concurrent and other dose groups. Fewer liver tumors and lymphosarcoma in multiple organs were observed in the treated females compared to the concurrent controls. The tumor incidence table of the report [Table 31; pages 267-273] is appended to

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the file copy of the DER. Historical control data on tumor incidence were not provided in the final report but were submitted [FAX dated 6/17/97] for comparison in response to the reviewer's request for historical control data on the incidence of adenoma in the lacrimal/Harderian gland, squamous cell carcinoma (malignant) in the mammary gland, and pituitary adenoma/carcinoma. Table 8 lists the historical control data submitted. The Registrant indicated that since the testing facility traditionally utilized the $B_6C_3F_1$ mouse, only limited historical control data are available on CD-1 mice and, therefore, data from the supplier, Charles River Laboratory, were included. Additionally, a description of the mammary tumor "squamous cell carcinoma" was provided, and it is stated that the revised, current terminology is "adenoacanthoma of the mammary gland". It is stated that it is an uncommon tumor in the CD-1 mouse.

Table 7. Microscopic Observations - Neoplastic [all mice]

Lesion/Sex/Dose [mg/kg/day]	0	100	300	1000
FEMALES				
LIVER n=	60			
hepatocellular adenoma	3 [5]♪	0	0	0♬
hepatocellular adenoma and/or carcinoma	4 [7]	0	0	0♬
MALES				
LIVER n=	60			
hepatocellular adenoma	3 [5]	14*[23]	5 [8]	5 [8]
FEMALES				
MULTIPLE ORGANS n=	42	45	40	40
lymphosarcoma, malignant, unknown	10 [24]	3 [7]⁑	2 [5]⁑	1*[3]
MALES				
LACRIMAL/HARDERIAN GLAND(S) n=	60	35	37	60
adenoma	1	1	0	3
FEMALES				
LACRIMAL/HARDERIAN GLAND(S) n=	60	18	14	60
adenoma	0	0	0	3
FEMALES				
ANY SITE n=	60	60	60	60
histiocytic sarcoma, malignant	1	1	3	4
FEMALES				
MAMMARY GLAND n=	60	18	14	60
squamous cell carcinoma, malignant, primary	0	0	0	1
FEMALES				
PITUITARY n=	59	18	15	57
adenoma, benign, primary	1	0	1	1
carcinoma, malignant, primary	0	0	0	1
adenoma and/or carcinoma	1	0	1	2

♪ [%]; ♬ significant linear trend by Cochran-Armitage trend test; * α<0.05 Yate's Chi-square pairwise test; ⁑ tissue not examined in all mice from low- and mid-dose mice; therefore, not used in statistical comparisons; data from pages 210, 239, 241, 248, 266, 267 of the report

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Table 8. Historical Control Data [CD-1 Mice]♪

Organ/Lesion/Sex	control	low	mid	high
MALES				
LACRIMAL/HARDERIAN GLAND(S)				
adenoma				
study 1a	1/50	0/19	0/15	2/50
study 4	5/45	5/44	4/51	4/41
cystadenoma				
study 2	4/50	0/25	0/33	1/50
adenoma and/or cystadenoma				
study 3	2/50	2/20	2/27	2/50
adenocarcinoma				
study 4	0/45	0/44	1/51	0/41
FEMALES				
LACRIMAL/HARDERIAN GLAND(S)				
adenoma				
study 1a	1/50	0/13	3/50	-/0
study 1b	1/45	-/0	0/47	-
study 4	4/44	4/48	2/43	4/42
cystadenoma				
study 2	0/50	0/10	1/15	3/50
adenoma and/or cystadenoma				
study 3	3/50	2/13	1/22	0/50
adenocarcinoma				
study 4	0/44	0/48	0/43	0/42
FEMALES				
MAMMARY GLAND				
adenoma				
study 1a	2/50	0/9	0/49	-/0
study 1b	0/49	-/0	0/47	-
study 2	0/50	0/11	0/15	1/50
study 4	2/53	0/50	1/47	0/53
adenocarcinoma				
study 1a	1/50	0/9	0/49	-/0
study 1b	0/49	-/0	0/49	-
study 2	0/50	0/11	0/15	0/50
study 4	5/53	0/50	3/47	5/53
carcinoma with or without metastasis				
study 3	2/50	0/11	0/21	0/49
keratoacanthoma				
study 4	0/53	0/50	0/47	1/53
FEMALES				
PITUITARY				
adenoma				
study 1a	1/49	0/12	2/47	-/0
study 1b	2/49	-/0	2/50	-
study 3	0/49	0/12	0/21	0/50
study 4	1/53	0/52	0/51	2/54
adenocarcinoma				
study 1a	0/49	0/12	0/47	-/0
study 4	1/53	0/52	0/51	0/54
adenoma/adenocarcinoma				
study 2	0/48	0/10	0/15	0/50
altered focus				
study 1a	0/49	0/12	2/47	-/0
focus altered cells				
study 1b	1/49	-/0	0/50	-
study 3	1/49	1/12	0/21	0/50
nodular hyperplasia				
study 4	2/53	1/52	0/51	0/54

♪ excessive mortality in study 1a [1996] at high dose; study 1b [1996] was an additional control, low-, and high [but lower] dose group; study 3 [1993] was an inhalation study; study 4 [1980]; data from page 3 of FAX, dated 6-17-97

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III. DISCUSSION

A. Following oral exposure of CD-1 mice to Fluroxypyr via the diet at dose levels up to 1000 mg/kg/day for 18 months, there were no adverse effects on survival or clinical signs in either sex at any dose level. The most common cause of death was systemic amyloidosis. Males at the high-dose level displayed a decreased body-weight gain throughout most of the study, with an overall gain that was 80% of the control. High-dose females displayed a slight [92% of control] decrease in body-weight gain compared to the control females. Food consumption was comparable among the groups of both sexes. The kidney is reported to be the target organ in both sexes. There were no adverse effects observed on any of the monitored hematology or ophthalmoscopy parameters in either sex. At the terminal sacrifice, there was a slight increase in the incidence of distended gall bladder in both sexes at the high-dose level [both macroscopically and microscopically] and a slight increase in the number of mice of both sexes with kidneys that were considered decreased in size. Organ weights, including kidneys, were comparable among the groups in both sexes. There was no apparent increase in the incidence of any tumor type in either sex.

B. Study deficiencies: None that would adversely affect study interpretation.

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