(9-29-97)

[FLUROXYPYR METHYLHEPTYL ESTER] PRENATAL DEVELOPMENTAL TOXICITY STUDY - RABBIT OPPTS 870.3700 [§83-3(b)]

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DATA EVALUATION RECORD

STUDY TYPE: Prenatal Developmental Study [rabbit]; OPPTS 870.3700 [§83-3 (b)]
DP BARCODE: D232217 SUBMISSION CODE: S515138
P.C. CODE: 128959 ID #: 062719-EIL STARANE F
REGISTRATION CASE NO.: 060640 CASWELL NO.: 463 O
TEST MATERIAL (PURITY): Fluroxypyr methylheptyl ester

SYNONYMS: ((4-amino-3,5-dichloro-6-fluoro-2-pyridinyl)oxy)acetic acid 1-methylheptyl ester; Fluroxypyr MHE, DOWCO*433 Ester

CITATION: Liberacki, A.B.; Breslin, W.J.; Quast, J.F. (1996). Fluroxypyr Methylheptyl Ester: Oral Gavage Teratology Study in New Zealand White Rabbits. The Toxicology Research Laboratory, Health and Environmental Sciences, The DOW Chemical Company. Laboratory Project Study ID K-137992-013, May 2, 1996. MRID 44080319. Unpublished.

SPONSOR: DowElanco

EXECUTIVE SUMMARY: Under the conditions of this developmental toxicity study [MRID 44080319], the administration of Fluroxypyr methylheptyl ester [95.8% a.i.] to 20 naturally-inseminated New Zealand female rabbits/group via gavage at dose levels of 0 [vehicle METHOCEL*A4M], 100, 500, and 1000 mg/kg/day from days 7 through 19 of gestation resulted in maternal toxicity at the high-dose level, as evidenced by an increased incidence of abortions. Body weight was comparable among the groups, but body-weight gains were decreased at the mid- and high-dose levels [not dose-related] mainly during the dosing period, which may be attributed to palatability. Corrected maternal body weight was comparable among the groups. Comparable pregnancy rates were observed among the groups, and there were no premature deliveries or does with 100% intrauterine deaths. All does had live fetuses at necropsy, and there were comparable numbers of corpora lutea, implantations, resorptions, and live fetuses among the groups. Both pre- and post-implantation losses were comparable among the groups. Fetal body weight was slightly decreased [97% of control] at the high-dose level compared to the concurrent control, but this may be attributed to the increased number of fetuses per doe at this dose level. There were no external, skeletal, or visceral anomalies or variations that could be attributed to treatment, and there was no treatment-related increase in visceral or skeletal malformations. Although there was an apparent increase in the incidence of a minor anomaly, retrocaval ureter, at the mid- and high-dose levels, its toxicological significance is doubtful.

The maternal/developmental LOEL is 1000 mg/kg/day, based on an increased incidence of abortions. The maternal NOEL is 500 mg/kg/day.

This guideline [§83-3(b)] prenatal developmental toxicity study in the rabbit is classified 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 methylheptyl ester;Fluroxypyr MHE
Description: dark green to black solid
Batch #: AGR283750
Source: DowElanco, Indianapolis, IN
Purity: 95.8% a.i. [an impurity, [redacted] was present at [redacted] by weight]
CAS #: 069377-81-7
[Structure]

2. Vehicle: 0.5% METHOCEL A4M
Description: aqueous vehicle
Lot/Batch #: not provided

3. Test animals: Strain: rabbit
Strain: New Zealand white
Age: time-mated females 5-6 months old
Weight: ≈3250 g on day 0 of gestation
Source: HRP, Inc., Kalamazoo, MI
Housing: individual
Diet: Certified Laboratory Rabbit Chow #5322, Purina Mills, Inc., St. Louis, MO. The rabbits received ≈2 oz of chow upon receipt and the amount of feed was increased incrementally by 2 oz/day up to a total of ≈8 oz/day.
Water: ad libitum
Environmental conditions: normal laboratory conditions
Acclimation period (P): at least 6 days

B. PROCEDURES AND STUDY DESIGN

1. In life dates - [not clear from report; Quality Assurance statement lists Study Initiation Date as August 31, 1995; the date of the audit of the Final Protocol is August 10, 1995 and the date of the audit of the protocol and study conduct is August 31, 1995. The Data and Draft report are listed as having been audited on March 20-25, 1995. The C-section dates listed on the individual animal data [Table B-1] are August 28-31, 1995 and September 7-9, 1995]
start: ≈ August 1, 1995; end: ≈ September 7, 1995

2. Mating: Adult females [≈5-6 months of age] were naturally mated with one buck of the same strain at HRP, Inc. and shipped to the testing facility on day 0 or 1 of gestation, at which time they were placed into individual cages and allowed to acclimate for ≈6 days prior to treatment. Day 0 body weights and records of mating pairs were provided by HRP, Inc. There was no other information provided about the mating procedure.

3. Animal Assignment: The time-mated rabbits were assigned randomly [using a computer-generated procedure designed to achieve similar body weights across experimental groups] to 4 groups of 20 does per group. Fluroxypyr MHE was administered via gavage at dose levels of 0 [aqueous vehicle, 0.5% METHOCEL A4M in a volume of 4 mL/Kg], 100, 500, and 1000 mg/kg/day. These dose levels represented Fluroxypyr acid equivalents of 0, 69, 346, and 693 mg/kg/day.

4. Dose selection rationale: The dose levels were based on 2 [one range-finding and one developmental toxicity] studies on Fluroxypyr acid [doses of 0, 300, 500, and 1000 mg/kg/day on days 6-18 and 0, 25, 100, and 400 mg/kg/day via gavage on days 6-19 of gestation, respectively] and a gavage teratology probe study on Fluroxypyr methylheptyl ester using doses of 0, 300, 500, 750, and 1000 mg/kg/day. **Range-finding study on Fluroxypyr acid:** Deaths occurred at 1000 mg/kg/day prior to scheduled necropsy and this group was terminated. A dose-related response to treatment characterized mainly by increased respiration rate, muscular weakness, and incoordination was observed at 500 and 1000 mg/kg/day. Fetal and placental weights were decreased at 500 mg/kg/day also. No effects were observed at 300 mg/kg/day.**Teratology study on Fluroxypyr acid:** Marked, treatment-related signs of toxicity [increased respiratory rate, ataxia, and muscular weakness early in the dosing period] were observed at 400 mg/kg/day and this group was terminated. There were no treatment-related signs of maternal toxicity and no treatment-related effects on reproductive or fetal parameters at dose levels up to 250 mg/kg/day. **Probe study on Fluroxypyr methylheptyl ester:** No significant differences were observed in maternal body weight/ gain, feed consumption, clinical signs, organ weights, or any reproductive parameters monitored at any dose level. The NOEL was 1000 mg/kg/day.

5. Dosage preparation and analysis

The test material, Fluroxypyr MHE, was administered as a suspension in an aqueous vehicle of 0.5% METHOCEL A4M, such that a dose volume of 4 mL/kg body weight yielded the targeted dose. The dose suspensions were mixed once prior to the start of the dosing period and once approximately halfway through the dosing regime. Analysis of all dosing suspensions from the first mix were performed to determine Fluroxypyr MHE concentrations prior to and following dosing. Stability of Fluroxypyr MHE in the vehicle was established for the use period, and the low and high dose suspensions from the first mix were analyzed for homogeneity prior to the start of dosing.

Results - The suspensions were found to contain the targeted [99% to 104%] concentrations, were stable during the dosing period, and all suspensions were found to be homogeneous [Tables 1 & 2, pages 25-26 of the report].

6. Dosage administration: All doses [0, 100, 500, 1000 mg/kg] were administered once daily via gavage on gestation days 7 through 19, in a dosing volume of 4 mL/kg of body weight/day. Dosing volumes were adjusted daily based on individual body weight.

C. OBSERVATIONS

1. Maternal Observations and Evaluations - The does were checked daily for alterations in behavior and demeanor. Body weights were recorded on days 0 at HRP, Inc., daily during the dosing period, and on days 20 and 28 of gestation. Food consumption was measured daily during the testing period beginning on gestation day 4. Surviving does were sacrificed [via an i.v. injection of a euthanasia solution [Beuthanasia-D Special] on day 28 of gestation, and a limited gross pathologic examination [necropsy] was performed. Any obvious gross pathologic alterations were recorded, and the weights of the liver, kidneys, and gravid uteri were recorded. Sections of liver with gallbladder, kidneys, and gross lesions were preserved, although microscopic examination was not performed. The uterine horns were exteriorized through an abdominal incision and (1) the number and position of the fetuses in utero, (2) the number of live and dead fetuses, (3) the number and position of resorption sites, (4) the number of corpora lutea, (5) the sex and body weight of each fetus, and (6) any gross alterations were recorded. The number of corpora lutea was not recorded for females that were not visibly pregnant at necropsy or for females having totally resorbed litters. The uteri of apparently non-pregnant rabbits were stained with a 10% aqueous solution of sodium sulfide and examined for evidence of early resorptions.

2. Fetal Evaluations - All fetuses were examined by dissection under a low power stereomicroscope for evidence of visceral alterations, which included a fresh examination of the brain. All fetuses were then preserved in alcohol, eviscerated, cleared, and stained with alizarin red-S and examined for skeletal alterations.

D. DATA ANALYSIS

1. Statistical analyses: doe body weight/gain, organ weights [absolute and relative], fetal body weights: Bartlett's test for equality of variances; based on outcome, a parametric or nonparametric analysis of variance [ANOVA] was performed, followed respectively by Dunnett's test or the Wilcoxon Rank-Sum test with a Bonferroni correction for multiple comparisons. Feed consumption: descriptive statistics [means ± SD]. Pre-implantation loss and resorptions among litters and the fetal population: censored Wilcoxon test with Bonferroni's correction. Number of corpora lutea, implants, and litter size: nonparametric ANOVA followed by the Wilcoxon Rank-Sum test with Bonferroni's correction. Pregnancy rates: Fisher's exact test. Fetal sex ratios: binomial distribution test. Nonpregnant females, females detected as pregnant following staining, and females having totally resorbed litters were excluded from the appropriate analyses.

2. Indices: Preimplantation loss was the only index calculated in the report:

$$\% \text{ preimplantation loss} = \frac{\#\text{ corpora lutea} - \#\text{ implantations}}{\#\text{ corpora lutea}} \times 100$$

corpora lutea

3. Historical control data: Historical control data [reproductive indices summary with # and % pregnant/maternal deaths, # pregnant (based on staining), # and % aborted/early deliveries/resorptions/litters with resorptions/dead fetuses, # totally resorbed litters, # corpora lutea/ implantation sites/fetuses per litter, sex ratio, gravid uterine weight, average fetal weight, % pre-implantation loss] were provided.

II. RESULTS

A. MATERNAL TOXICITY

1. Mortality and Clinical Observations: There was an increased incidence of abortion at the mid- [one on day 25] and high-dose [three on days 22, 25, and 25] levels compared to the concurrent and historical controls. One death occurred on day 20 at the high-dose level, but this was attributed to gavage error. All other dams survived until study termination. With the exception of the abortions, there were no treatment-related adverse clinical signs observed. Two of the three high-dose does that aborted displayed decreased food consumption and body-weight loss prior to the abortions. No abortions are listed in the summary historical control data [Table 11, page 36], but 2 of the 16 studies listed in Table A-7 [Historical Control] of the report [see Discrepancies section at end of DER] list 1 abortion each [1/22 does and 1/18 does].

2. Body Weight: Body weight among the groups was comparable throughout the study, but body-weight gains were variable throughout [Table 1]. Prior to dosing, the does in each treatment group displayed larger body-weight gains than the control group [105-125% of control]. During the first 16 days of dosing, the high-dose does displayed decreased gains [73-87% of control] compared to the control, and the mid-dose does displayed decreases [53-61% of control] during the 10-20 day period, although no dose-response was observed [Table 1]. The low-dose does also displayed a decreased body-weight gain during days 13 and 16 of the dosing period. Both the mid- and high-dose does displayed an overall decrease in body-weight gain during the dosing period but there was no dose response. Corrected body weight was comparable among the groups.

Table 1. Body Weight [% of control]/Gain [g(% of control)] During Gestation

Time/Dose (mg/kg/day)	0	100	500	1000
BODY WEIGHT♠				
day 0	100	101	100	100
day 7	100	101	100	101
day 10	100	101	100	100
day 13	100	102	99	100
day 16	100	101	98	100
day 20	100	102	98	100
day 28	100	102	99	100
BODY WEIGHT GAIN ♪				
day 0-7	133.7	167.4 [125]	140.2 [105]	152.1 [114]
day 7-10	33.8	40.4 [120]	34.7 [103]	25.2 [75]
day 10-13	72.5	84.0 [116]	42.2 [58]	62.8 [87]
day 13-16	110.5	85.4 [77]	66.9 [61]	81.1 [73]
day 16-20	32.9	63.2 [192]	17.4 [53]	34.0 [103]
day 20-28	134.7	129.3 [96]	148.4 [110]	147.5 [110]
day 7-20	253.3	273.0 [108]	161.2 [64]	202.4 [80]
day 0-28	520.3	569.8 [110]	490.4 [94]	582.3 [112]
CORRECTED BODY WEIGHT [n=]	3287.3 [20]	3360.8 [20]	3248.1 [19]	3331.2 [15]

♠ calculated by reviewer using data from page 32 of report; ♪ data from page 33 of report;
♬ from page 23 of report;

3. Food Consumption - After the first three days of dosing, food consumption was decreased [Table 2] for the mid- and high-dose does [no dose response]. The mid-dose does displayed the lowest food consumption. During days 26 to 28, comparable food consumption was observed among the groups.

Table 2. Food Consumption [% of control]♦

Day/Dose	100 mg/kg/day	500 mg/kg/day	1000 mg/kg/day
6-7	102	98	102
7-8	101	101	96
8-9	104	100	99
9-10	105	94	95
10-11	96	92	97
11-12	105	91	97
12-13	104	87	96
14-15	102	85	90
16-17	100	84	89
18-19	105	83	92
24-25	102	84	88
25-26	95	81	78
26-27	96	103	100
27-28	106	104	97

data from page 30-31 of the report;
♦ (% of control, calculated by reviewer)

4. Gross Pathology - There were no treatment-related gross pathology findings in any of the does surviving to scheduled sacrifice. The mid-dose doe that aborted one pup had decreased ingesta and a pale gallbladder, and the uterus contained 9 implants, two of which were early resorptions and the rest were normal for gestational age. One high-dose doe aborted 9 pups, and the uterus contained no additional fetuses and all tissues were normal. Another high-dose doe aborted six

fetuses, and the liver was pale and exhibited an accentuated lobular pattern. The uterus did not contain additional fetuses. Another high-dose doe that aborted one fetus had 8 additional fetuses retained in the uterus, all normal for gestational age. All other tissues were normal. The high-dose doe that was found dead was pregnant [uterus contained 10 fetuses, all appearing normal], and the lungs were dark and mottled, which is consistent with aspiration of the test material. Regarding the incidence of abortion in this study, incidence at the mid-dose level [1 in 20 does] is within the historical control range, although in only 2 of the 16 studies referenced did an abortion occur [January, 1991 (1 in 19 does) and April, 1991 (1/17 does)].

5. Cesarean Section Data - Pregnancy rate was comparable among the groups, but the high dose had the fewest number of litters [Table 3]. There were 4 abortions as described above, but there were no litters that were totally resorbed. All does had live fetuses at necropsy, and there were comparable numbers of corpora lutea, implantations, and live fetuses per litter, with the high-dose does displaying the greatest number per litter. There were no dead fetuses. There were fewer does at the low- and high-dose levels with resorptions than the control and mid dose, but the high-dose does displayed a slight increase [0.67 vs 0.5] in the mean number of resorption per doe compared to the concurrent control but within the historical control range [0.1-1.1]. When only litters with resorptions are considered, both the low- and high-dose groups displayed a greater number of resorptions per litter [2] than the control [1.25] and mid-dose [1.29]. When compared to the historical control, only 2 of the 16 studies had an incidence of ≥2; the mean being 1.49 [range 1-2.8]. Pre- and post-implantation losses were comparable among the groups.

Table 3: Cesarean Section Observations

GROUP:	0 mg/kg/day	100 mg/kg/day	500 mg/kg/day	1000 mg/kg/day
# Females mated	20	20	20	20
# Pregnant Females	20	20	20	19
Pregnancy Rate (%)	100	100	100	95
Maternal Wastage				
#Died	0	0	0	1
#Died/pregnant	0	0	0	1
#Died/Non pregnant	0	0	0	0
#Aborted	0	0	1	3
#Premature Delivery	0	0	0	0
# Females with 100% intrauterine deaths	0	0	0	0
# Females with live fetuses at necropsy (%)	20 (100)	20 (100)	19 (95)	15 (79)
Total # Corpora Lutea♦	194	207	204	163
Corpora Lutea/dam	9.7	10.4	10.7	10.9
Total # Implantations♦	176	172	177	148
Implantations/Dam	8.8	8.6	9.3	9.9
Total # Live Fetuses♦	166	168	168	138
Live Fetuses/Dam	8.3	8.4	8.8	9.2
% of implantations♦	94.3	97.7	94.9	93.2
Total # Resorptions♦	10	4	9	10
Early♦	8	3	9	6
Late♦	2	1	0	4
Resorptions/Dam♦	0.5	0.2	0.47	0.67
# Litters w/ resorptions (%)	8(40)	2(10)	7(37)	5(33)
Resorptions/litters w/resorpt.	1.25	2.0	1.29	2.0
Total # Dead Fetuses	0	0	0	0
Postimplantation Loss (%)♦	6.37	0.62	0.47	6.37
Preimplantation Loss (%)♦	9.51	16.3	11.2	8.46
Litter Weight (gm)	-	-	-	-
Mean Fetal Weight [gm]	37.3	38.3	37.0	36.3
Mean Male Weight [gm]♦	37.5	39.4	37.5	36.4
Mean Female Weight [gm]♦	37.2	37.2	37.0	36.2
Sex Ratio (% Male)♦	45.8	48.8	45.2	52.9
Mean # Males♦	3.8	4.1	4.0	4.9
Mean # Females♦	4.5	4.3	4.8	4.3
Gravid Uterus (gm)[% of control]	466.7	476.5	490.4	508.2[109]
Mean Weight of Placentas (gm)	-	-	-	-
Corrected Doe Body Weight (gm)♪	3287.3	3360.8	3248.1	3331.2
Net Doe Weight Change From Day 0♦	38.6	108.1	-2.9	76.7

data from page 35 of the report; ♦ calculated by reviewer from data on pages 128-239 of report; ♪ data from page 32 of report; - not provided;

8

B. DEVELOPMENTAL TOXICITY

1. External Examination - Fetal body weight [Table 4] was slightly lower [97% of control] than the control value for both sexes at the high-dose level but within the historical control range [31.8-40.3 grams]. This difference may be attributed to the fact that the high-dose group displayed the largest number of fetuses [9.2 vs 8.3 in the control] per doe. There were no treatment-related external variations or malformations reported.

Table 4. Fetal Body Weight [grams]

Dose/Sex	0 mg/kg	100 mg/kg	500 mg/kg	1000 mg/kg
males♪	37.5	39.4	37.5	36.4
females	37.2	37.2	37.0	36.2
♪ combined	37.3	38.3	37.0	36.3

♪ calculated by reviewer using data from pages 128-239 of the report; data from page 35 of the report

2. Visceral/skeletal Examinations - **ANOMALIES/VARIATIONS** There was a statistically significant increase in the incidence of a minor fetal variation, retrocaval ureter, at the limit dose compared to the concurrent control group, and the incidence is outside the historical control range also [Table 5]. The author noted that the incidence of this variation has been increasing recently at the testing facility [historical control data on pages 75-126 of the report]. Of the 16 studies cited in the historical control data, which were performed from April, 1990 to February, 1994 [4 inhalation, 12 gavage], the 3 most recent display the highest incidences: June, 1993 gavage study [10 fetuses (7.3%) in 6 litters (33%)]; January, 1994 gavage study [9 fetuses (6.8%) in 6 litters (32%)]; and February, 1994 gavage study [6 fetuses (5.1%) in 5 litters (33%)]. **MALFORMATIONS** All groups displayed malformations, but there was no apparent relationship to treatment [Table 6]. The number of fetuses with malformations in each group was 3, 2, 4, 2 in the control, low-, mid-, and high-dose groups, respectively.

Table 5. Visceral Findings [# pups/# litters]

Group/Variation	0 mg/kg/day	100 mg/kg/day	500 mg/kg/day	1000 mg/kg/day	Historical Control
URETER					
retrocaval ureter					
# fetuses [%]	3 [1.8]	6 [3.6]	12 [7.1]	11 [8.0]*	0-10♪ [0-7.3]
# litters [%]	2 [10]	2 [10]	7 [36.8]	7 [46.7]	0-6♪ [0-33]
# fetuses examined viscerally	166	168	168	138	1993
# litters examined viscerally	20	20	19	15	272

data from Table 12, pages 37-38 of the report; ♪ from 1993 study with 137 fetuses and 18 litters; * $p<0.05$

9

Table 6. Visceral/Skeletal Malformations [# pups/# litters]

Group/Variation	0 mg/kg/day	100 mg/kg/day	500 mg/kg/day	1000 mg/kg/day	Historical control
BRAIN					
dilated cerebral ventricles					
# fetuses [%]	1 [0.6]	0	0	0	fetal [0-2.3%]♪
# litters [%]	1 [5]	0	0	0	litter [0-5%]♪
GREAT VESSELS					
retroesophageal subclavian					
# fetuses [%]	1 [0.6]	1 [0.6]	0	1 [0.7]	fetal [0-2.3%]
# litters [%]	1 [5]	1 [5]	0	1 [6.7]	litter [0-15.8%]
LUNGS					
missing diaphragmatic lobe					
# fetuses [%]	0	0	1 [0.6]	0	fetal [0-6.3%]
# litters [%]	0	0	1 [5.3]	0	litter [0-33%]
diaphragmatic hernia					
# fetuses [%]	0	0	1 [0.6]	0	fetal [0-0.5%%]
# litters [%]	0	0	1 [5.3]	0	litter [0-4.8%]
RIBS					
fused					
# fetuses [%]	1 [0.6]	0	0	0	fetal [0-2.4%]
# litters [%]	1 [5]	0	0	0	litter [0-15.4%]
forked					
# fetuses [%]	0	1 [0.6]♦	1 [0.6]♦	0	fetal [0]
# litters [%]	0	1 [5]	1 [5.3]	0	litter [0]
missing					
# fetuses [%]	0	1 [0.6]♦	1 [0.6]♦	0	fetal [0-0.8%]♪
# litters [%]	0	1 [5]	1 [5.3]	0	litter [0-%]♪
extra cervical					
# fetuses [%]	0	0	1 [0.6]	0	fetal [0-1.2%]♪
# litters [%]	0	0	1 [5.3]	0	litter [0-7.7%]♪
VERTEBRAE					
hemivertebra					
# fetuses [%]	0	1 [0.6]♦	1 [0.6]♦	1 [0.7]	fetal [0-2.4%]
# litters [%]	0	1 [5]	1 [5.3]	1 [6.7]	litter [0-15.4%]
fused					
# fetuses [%]	0	0	1 [0.6]	0	fetal [0-0.6%]♪
# litters [%]	0	0	1 [5.3]	0	litter [0-4.8%]♪
# fetuses examined	166	168	168	138	1993
# litters examined	20	20	20	15	272

data from Table 12 [pages 37-40] and Table A-7 [pages 75-239] of the report; ♪ observed in 1 out of 16 studies; ♦ same fetus

III. DISCUSSION

Abortions occurred in one mid-dose and three high-dose does, and one death due to gavage error occurred at the high dose. All other dams survived until study termination. With the exception of the abortions, there were no treatment-related adverse clinical signs observed. Two of the three high-dose does that aborted displayed decreased food consumption and body-weight loss prior to the abortions. Body weight was comparable among the groups throughout the study, but the mid- and high-dose does displayed a decreased body-weight gain compared to the control during the dosing period, although there was no dose response. Food consumption was decreased compared to the control for the mid- and high-dose does following the start of dosing but the decrease was not dose-related and may have been due to palatability. Corrected body weight was comparable among the groups. Comparable pregnancy rates were observed among the groups, and there were no premature deliveries or does with 100% intrauterine deaths. All does had live fetuses at necropsy, and

there were comparable numbers of corpora lutea, implantations, resorptions, and live fetuses among the groups. Both pre- and post-implantation losses were comparable among the groups. Fetal body weight was slightly decreased at the high-dose level compared to the concurrent control, but there were a greater number of fetuses per doe at the high-dose level, which could explain this apparent decrease. There were no external or skeletal anomalies or variations that could be attributed to treatment, and there was no treatment-related increase in visceral or skeletal malformations. There was a slight increase in the incidence of a minor fetal variation [retrocaval ureter] at the mid- and high-dose levels compared to the concurrent and historical controls, but statistical significant was attained only at the high-dose level. The author indicated that the incidence of this anomaly in control rabbits at the testing facility has increased from the historical trend and, given this trend and the lack of any other effects on embryonal/fetal parameters, along with the absence of any such effects noted in a rabbit developmental toxicity study on Fluroxypyr acid, the toxicological significance of the finding is doubtful. Fluroxypyr methylheptyl ester does not appear to be a developmental toxicant in rabbits at dose levels up to the limit dose [1000 mg/kg/day]. It does, however, appear to have reproductive effects, as evidenced by the incidence of abortions observed at the mid- and high-dose levels. Although the incidence [1/20 does] at the mid-dose is within the historical control range, in only 2 of the 16 studies referenced did an abortion occur [1 out of 22 does and 1 out of 18 does], and the mean incidence at the testing facility is 0.7% [2 out of 272 does].

C. STUDY DEFICIENCIES: None that would impact negatively on the interpretation of the study results. It is not evident to this reviewer how Table 11 [Historical Control-Reproductive Indices Summary] relates to Table A-7 [Historical Control-Reproductive Indices]. For example, in Table 11, the number of abortions is listed as 0, but in Table A-7, 2 studies list 1 abortion each and the maximum number is listed as 1. Also, the maximum number bred is listed as 45 in Table 11 and 28 in Table A-7, and the maximum number of resorptions/litter is listed as 1.9 in Table 11 and 1.1 in Table A-7. One apparent error is noted in Table 11: average fetal body weight is listed as ≈5.3 grams. Average fetal body weight in Table A-7 is 37.94 grams, and in the current study it was ≈37 grams. Several discrepancies were noted in the Quality Assurance Statement, but these were resolved by communications between reviewer and Registrant.

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

12

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