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DATA EVALUATION REPORT

TEPRALOXYDIM

Study Type: DEVELOPMENTAL – RABBIT (83-3b)

MRID 44496404

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

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DATA EVALUATION RECORD

STUDY TYPE: Developmental Toxicity - Rabbit [OPPTS 870.3700 (§83-3b)]

DP BARCODE: D243962, D257665
P.C. CODE: 121005

SUBMISSION CODE: S538735
TOX. CHEM. NO.: None

TEST MATERIAL (PURITY): Reg. No. 191 819 (Tepraloxydim) (93.0% a.i.)

SYNONYMS: none

CITATION: Hellwig, J. (1995) Study on the prenatal toxicity of Reg. No. 191 819 in Himalayan rabbits after oral administration (gavage). BASF Aktiengesellschaft, Department of Toxicology, D-6700 Ludwigshafen/Rhein, Germany. Project No. 40R0268/92086, July 5, 1995. MRID 44496404. Unpublished.

SPONSOR: BASF Abteilung Toxikologie, Department of Toxicology, Ludwigshafen, Germany

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 44496404), 15 presumed pregnant Himalayan rabbits (outbred strain of Chbb: HM) per group were administered Tepraloxydim (93.0% a.i.) by gavage at doses of 0, 20, 60, or 180 mg/kg/day on gestation days (GD) 7-19, inclusive. The controls were given vehicle (0.5% aqueous carboxymethylcellulose) only for the same dosing period. On GD 29, all does were sacrificed, necropsied to assess gross pathology, and uteri and ovaries were removed. All fetuses were sexed, weighed, and examined for external malformations/variations prior to sacrifice. All of the fetuses were opened and checked viscerally then, if indicated, heads were removed and placed in Bouin's fixative and sectioned for examination of malformations/variations of the skull. The eviscerated fetuses (some without heads) were fixed in ethanol, further processed, stained, and examined for skeletal malformations/variations and retardations.

No compound-related deaths, abortions, or clinical signs of toxicity were observed throughout the study period. There were no statistically or biologically significant gross necropsy observations at maternal sacrifice. At the 180 mg/kg/day dose level, there was a statistically significant ($p \leq 0.05$) reduction in body weight gain (57.0%) during GD 14-16 and a 91% reduction in body weight gain throughout the treatment period (GD 7-19) with recovery during the post-treatment period (GD 19-29). There was also a treatment-related decrease in food consumption (13.3%) during the treatment period with recovery during the post-treatment period that correlated with the observed

observed reduced body weight change during the same period. No treatment-related maternal changes were noted at 20 or 60 mg/kg/day.

Therefore, based on reduction in mean body weight and food consumption during the treatment period, the maternal toxicity LOAEL is 180 mg/kg/day and the maternal toxicity NOAEL is 60 mg/kg/day.

Treatment with Tepraloxydim did not cause any statistically significant or treatment-related changes in gestational or cesarean section parameters at any treatment level. No statistically significant or treatment-related differences in external malformations/variations, visceral malformations/variations, or skeletal malformations/variations/ossification changes were observed in fetuses at any treatment level including controls.

Therefore, based on no observed adverse developmental effects, the developmental toxicity LOAEL is undetermined and the developmental toxicity NOAEL is ≥180 mg/kg/day.

This study is classified as **Acceptable/Guideline** and satisfies the guideline requirement for a developmental toxicity study in rabbits [OPPTS 870.3700 (§83-3b)]. No deficiencies were noted which would adversely affect the interpretation of this study.

COMPLIANCE: Signed and dated Good Laboratory Practice, Quality Assurance, Data Confidentiality, and Flagging statements were included.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: Tepraloxydim (Reg. No. 191 819)

   Description: light-brown powder
   Batch No.: N41
   Purity: 93.0% a.i.
   Stability of compound: not provided
   CAS No.: 149979-41-9

2. Vehicle and/or positive control

   Tylose® CB 30,000; purified carboxymethylcellulose (0.5% aqueous solution; HOECHST AG, Frankfurt/Main, Germany) was used as the vehicle and negative control. No positive control was used in this study.

3. Test animals

Species: rabbit
Strain: Himalayan (Chbb: HM)
Age and weight at study initiation: 21-29 weeks of age; 2,709 g mean weight on GD 0
Source: Karl Thomae, Biberach an der Riss, Germany
Housing: Animals were housed individually in suspended stainless steel cages with wire-mesh bottoms.
Diet: Pelleted Kliba maintenance diet type 23-341-4 (KLINGENTALMÜHLE AG, Kaiseraugst, Switzerland) was available *ad libitum*.
Water: Tap water was available *ad libitum*.
Environmental conditions:
Temperature: 20-24°C
Humidity: 30-70%
Air changes: not provided
Photoperiod: 12-hour light/dark
Acclimation period: ≥5 days

B. PROCEDURES AND STUDY DESIGN

This study was designed to assess the developmental toxicity potential of Tepraloxydim when administered by gavage to rabbits on GD 7-19, inclusive.

1. In life dates

Start: November 8, 15, or 22, 1993; end: December 7, 14, or 21, 1993

2. Mating

Virgin female Himalayan rabbits were impregnated by artificial insemination using pooled semen collected from Himalayan males obtained from the same supplier as the females. Approximately 1 hour before insemination, does were injected intramuscularly with a synthetic hormone which stimulates the anterior lobe of the pituitary to release LH and FSH (Receptal®, Hoechst AG, Frankfurt/Main, Germany). The day of insemination was considered GD 0.

3. Animal assignment

Animal assignment and dose selection is presented in Table 1. Assignment of animals was randomized by weight using combinatorial algorithms.

TABLE 1. Animal assignment		
Treatment Group	Dose (mg/kg/day)	Number Assigned
Control	0	15
Low Dose	20	15
Mid Dose	60	15
High Dose	180	15

Data taken from page 23, MRID 44496404.

4. Dose selection rationale

Doses were selected on the basis of a range-finding study (Project No. 20R0459/91092). Approximately 3-4 pregnant Himalayan rabbits per group were administered Tepraloxydim in 0.5% aqueous carboxymethylcellulose by gavage at 0, 150, 300, or 600 mg/kg/day on GD 7-19, inclusive. Body weight and food consumption were monitored and animals were checked daily for mortality and clinical signs of toxicity. Prior to sacrifice on GD 20, blood and urine samples were taken for hematology, clinical chemistry, and urinalysis. Gross pathological assessment was conducted at necropsy and the liver and kidneys of each doe were weighed. Only limited developmental toxicity data were obtained.

Food consumption was significantly decreased throughout the treatment period at 600 mg/kg/day and mean body weights were significantly lower than controls on GD 16, 19, and 20. Body weight gains were reduced throughout the treatment period. Corrected body weight was also reduced. One death occurred on GD 18 and clinical signs of toxicity including poor general appearance, bloody bedding, piloerection, urine soiled fur, and/or no defecation or soft feces, were observed in all does. Relative liver weights were increased as were absolute and relative kidney weights. Necropsy revealed multiple ulcerations of the stomach mucosa in all does and pale or light brown-gray kidneys in 2 does. There was complete embryolethality and mean uterine weights were, consequently, significantly reduced.

At 300 mg/kg/day, food consumption was significantly reduced throughout the treatment period during GD 6-13, absolute body weight was significantly reduced on GD 19 and 20, and mean body weight gains were statistically significantly reduced throughout the treatment period. Corrected body weight gain values were also reduced. Clinical signs of toxicity included 2 does with bloody bedding and 3 does with no defecation during the treatment period. There was complete embryolethality and mean uterine weights were, consequently, significantly reduced .

Adverse changes in hematology and clinical chemistry parameters observed at 600 and 300 mg/kg/day were considered a consequence of the reduced general state of does at sacrifice.

At 150 mg/kg/day, food consumption, body weight gain, and corrected body weight gain were reduced during the treatment period although not significantly. There were no overt, treatment-related effects on gestational parameters and uterine contents. One doe had a postimplantation loss of 50%.

Based on the range-finding study results, the study author selected 0, 20, 60 and 180 mg/kg/day as the treatment levels for the main study.

5. Dosing

All doses were administered daily during GD 7-19 in a volume of 10.0 mL/kg of body weight/day. Daily doses were based on the initial individual body weights on GD 7 and were not adjusted for daily body weight changes.

6. Dose solution preparation and analysis

Dosing solutions were prepared separately by homogenizing Tepraloxydim in 0.5% aqueous carboxymethylcellulose (w/v) to give nominal concentrations of 2.0, 6.0, or 18.0 mg/mL. The dosing solutions were prepared fresh daily and homogeneity during dosing was maintained by constant stirring on a magnetic stirrer. The actual content of active ingredient in each dosing solution was analyzed in duplicate for samples prepared near the beginning and end of the study. The stability of the test article in 0.10128 and 1,012.8 µg/mL aqueous solutions was determined after up to 14 days of storage at room temperature prior to initiation of the experiment. Homogeneity was analyzed during a previous study using 6 samples each of 1,500 mg/100 mL and 6,000 mg/mL suspensions in 0.5% aqueous carboxymethylcellulose; it was not stated whether the samples were taken from the top, middle, and bottom of the solutions.

Results –

Stability analysis: Samples taken for stability analysis of aqueous solutions ranged from 94.9-102.3% of initial concentration for 0.10128 µg/mL solutions and 96.8-105.8% of initial concentration for 1,012.8 µg/mL solutions during the 14-day stability testing period; within the ±10% allowable range.

Homogeneity analysis: The analytical concentrations of the multiple samples taken for homogeneity varied by less than 5%.

Concentration analysis: The mean actual concentrations of the 2.0, 6.0, and 18.0 mg/mL suspensions were 88.4-94.1%, 89.5-95.7%, and 93.2-95.6%, respectively, of nominal.

The analytical data indicated that the dosing solutions were stable for up to 14 days at room temperature and that the variance between nominal and actual dosage to the study animals was acceptable. Concentrations of one low-dose sample and one mid-dose sample less than 10% of nominal are not considered to compromise the integrity of this study.

C. OBSERVATIONS

1. Maternal observations and evaluations

All animals were observed at least once daily for clinical signs of toxicity and mortality. Maternal body weights were recorded on GD 0, 2, 4, 7, 9, 11, 14, 16, 19, 21, 23, 25, and 29. Body weight changes were calculated from these data. Food consumption was recorded daily throughout the experimental period. Net body weight gain was calculated as the terminal body weight minus the uterine weight at sacrifice and minus the body weight on GD 7. On GD 29 does were sacrificed by intravenous injection of pentobarbital and cesarean sections were performed as well as gross pathology of the thoracic and abdominal cavities. The uteri and ovaries were removed and the weights of uteri were recorded before opening. Ovaries were examined for numbers of corpora lutea and uteri were examined for total implantation sites and live, dead, and resorbed fetuses. Preimplantation and postimplantation losses were calculated for each treatment group.

2. Fetal evaluations

All fetuses were sexed, weighed, and examined for external malformations/variations prior to sacrifice by CO_2 asphyxiation. After opening, the organs of the abdominal and thoracic cavities were examined prior to removal and sex was verified by internal observations. The heart and kidneys were removed for sectioning, the eviscerated fetuses were skinned, and the remainder of the carcass fixed in ethanol. After brief fixation, fetal heads were examined by cross sectioning the skull. If anophthalmia, microphthalmia, hydrocephalus, or cleft palate were observed, affected heads were removed, fixed in Bouin's solution, processed, and examined by transverse sectioning using the method of Wilson. After further ethanol fixation, the skeletons (some possibly minus skulls) were stained and examined for skeletal malformations/variations and retardations using a modification of the method of Dawson.

D. DATA ANALYSIS

1. Statistical analysis

Body weight, body weight changes, food consumption, maternal and fetal parameters, and cesarean section data were compared between treatment and control groups using Dunnett's two-sided test. Female mortality, pregnancy at sacrifice, and litters with fetal findings were compared pairwise using a one-sided Fisher's exact test. Fetal malformations, variations, and retardations were compared using the one-sided Wilcoxon test to compare data for each dose group to controls. The level of significance was set at a confidence interval of 95 or 99% ($p \leq 0.05$ or 0.01).

2. Historical control data

These data were provided to allow comparison with concurrent controls.

II. RESULTS

A. MATERNAL TOXICITY

1. Mortality and clinical signs

No treatment-related deaths or abortions occurred during the study. No clinical signs of toxicity were observed in any treatment group including controls.

2. Body weight

Body weight and body weight gain data are listed in Table 2. There were no statistically significant differences in mean absolute body weights between the treated groups and the control group during the gestational period. However, at the 180 mg/kg/day dose level, there was a statistically significant ($p \leq 0.05$) body weight loss (57.0%) during GD 14-16 compared to controls. Likewise there was a 91% decrease in body weight gain during the treatment period (GD 7-19) compared to controls with apparent post-treatment recovery; due to the large variation in individual values, statistical significance was not attained for this interval. There were no treatment-related changes in body weight or body weight gain at the 20 or 60 mg/kg/day treatment levels. No differences in net body weight gain at GD 7-29 or carcass weights were observed at any dose level compared to controls.

TABLE 2: Maternal body weight, body weight gain, and food consumption during gestation				
Gestational day	Dose in mg/kg/day (# of pregnant does)			
	0 (15)	20 (15)	60 (15)	180 (15)
Mean body weight (g)				
0	2707	2709	2702	2716
2	2729	2728	2724	2743
4	2725	2731	2720	2733
7	2714	2710	2704	2725
9	2708	2713	2684	2704
11	2703	2710	2679	2703
14	2727	2745	2697	2716
16	2768	2774	2731	2733
19	2777	2789	2726	2731
21	2773	2779	2731	2748
23	2807	2830	2771	2788
25	2876	2886	2836	2850
29	2970	2993	2948	2957
Mean body weight gain (g)				
0-7	6.2	1.4	1.9	9.9
7-19	63.3	78.6	21.7	5.7
19-29	193.5	204.3	222.5	225.9
0-29	262.9	284.3	246.0	241.5
Mean food intake (g/dam/day)[a]				
0-7	114.0	110.2	111.2	112.2
7-19	90.3	91.1	85.5	78.3
19-29	109.0	112.2	110.5	121.7
0-29	102.4	103.0	100.3	101.5

Data taken from Tables 004, 005, 006, and 009, pp. 58, 59, 60, and 63, respectively, MRID 44496404.
[a]Mean of means.

3. Food consumption

Food consumption is summarized in Table 2. There was a significant decrease ($p \leq 0.05$) in mean food consumption at 180 mg/kg/day on GD 10-11 (16.6%) and 12-13 (19.9%) compared to controls. The overall decrease in food consumption (13.3%) during the treatment period (GD 7-19) was not statistically significant but was considered treatment-related. Recovery of appetite at 180 mg/kg/day was indicated, during the post-treatment period (GD 19-29), by an 11.7% increase in food consumption compared to controls. Overall (GD 0-29), the recovery from reduced food consumption during the treatment period appeared complete at 180 mg/kg/day. No statistically significant or treatment-related differences in food consumption were noted at 20 or 60 mg/kg/day compared to controls.

4. Gross pathology

There were no statistically significant ($p \leq 0.05$) or treatment-related gross necropsy observations at maternal sacrifice.

5. Cesarean section data

Cesarean section data are summarized in Table 3. There were no statistically significant or treatment-related differences in cesarean section parameters at any treatment level compared to controls. One fetal death occurred in the control group.

TABLE 3. Cesarean section observations in rabbits

Observations	Dose in mg/kg/day			
	0	20	60	180
No. Animals Assigned	15	15	15	15
No. Animals Pregnant	15	15	15	15
Pregnancy rate (%)	100	100	100	100
Maternal Mortality	0	0	0	0
Delivered Early/Aborted	0	0	0	0
Total Corpora Lutea	130	133	124	134
Corpora Lutea/Doe	8.7±1.23	8.9±1.36	8.3±1.33	8.9±1.83
Total Implantations	115	114	105	119
Implantations/Doe	7.7±1.80	7.6±2.90	7.0±1.93	7.9±1.83
Preimplantation Loss (%)	12.0±12.58	15.9±26.37	15.7±18.73	10.9±11.06
Postimplantation Loss (%)	8.3±17.12	8.5±12.54	8.7±9.50	14.9±20.28
Total Resorptions/Doe (early and late)	0.5±1.06	0.8±1.32	0.6±0.63	1.1±1.28
Gravid Uterine Weight (g)	387.6±100.57	379.6±120.78	366.0±100.85	371.0±103.29
Carcass Weight (g)[a]	2582.8±139.14	2613.2±121.71	2582.3±109.01	2586.1±118.86
Net weight change from GD 7[b] (g)	-130.8	-96.7	-121.9	-139.3
Does with Viable Fetuses	15	15	15	15
Total Live Fetuses	106	102	96	103
Live Fetuses/Litter	7.1±2.12	6.8±2.57	6.4±1.96	6.9±2.42
Live Males/Litter	3.6±2.44	2.9±1.39	3.3±1.88	3.3±1.40
Live Mean Fetal Weight (g)	40.5±3.42	41.8±4.82	41.9±3.32	39.6±4.15
Fetal deaths	1	0	0	0
Sex Ratio (% Male)	50.9	43.1	52.1	48.5
Mean placental wt. of viable fetuses (g)	4.3±0.49	4.8±0.89	4.8±0.55	4.7±0.75

Data taken from Tables 010, 013, 014, 015, and 016, pp. 64 and 67-70; MRID 44496404.
[a]Carcass weight = terminal body weight minus gravid uterine weight.
[b]Net weight change from GD 7 = carcass weight minus GD 7 body weight (treatment and post-treatment).

B. DEVELOPMENTAL TOXICITY

The number of fetuses(liters) examined in the control, low-, mid-, and high-dose groups was 107(15), 102(15), 96(15), and 103(15), respectively. There were no statistically significant ($p \leq 0.05$) external, visceral, or skeletal malformations/variations in the fetuses or litters at any treatment level compared to controls. There was also no indication of altered fetal growth at any treatment level.

1. External examination

There were no statistically significant ($p \leq 0.05$) or treatment-related external malformations or variations observed in fetuses at any dose level as shown in Table 4. At 180 mg/kg/day, one fetus had a herniated umbilicalis, but was not considered treatment-related. External variations were randomly distributed between the control and treatment groups. Pseudoankylosis was observed in one fetus in each of 2, 2, and 1 litters in the 0, 20, and 60 mg/kg/day groups and bent toes of the left hind foot were observed in one high-dose fetus. The external variations observed were considered random and sporadic and not treatment-related.

TABLE 4: Summary of fetal external malformations/variations

Observations	Dose in mg/kg/day			
	0	20	60	180
Examined #Fetuses (#Litters)	107 (15)	102 (15)	96 (15)	103 (15)
External malformations #Fetuses (#litters) Hernia umbilicalis	 0 (0) 0 (0)	 0 (0) 0 (0)	 0 (0) 0 (0)	 1 (1) 1 (1)
External variations #Fetuses (#litters) Pseudoankylosis of forelimb Toes of hindlimb bent	 2 (2) 2 (2) 0 (0)	 2 (2) 2 (2) 0 (0)	 1 (1) 1 (1) 0 (0)	 1 (1) 0 (0) 1 (1)

Data taken from Tables 017-019, pp. 71-73, MRID 44496404.

2. Visceral examination

The results of visceral examination are shown in Table 5. No statistically significant visceral malformations were observed in any treatment group, compared to controls. A herniated diaphragm, observed in one high-dose fetuses was considered spontaneous. A range of visceral variations was observed throughout the treatment groups including controls (12-17% of fetuses and 40-73% of litters). Visceral variations observed included separated origin of carotids, heart with traces of interventricular foramen/septum membranaceum, hypoplasia of the gallbladder and dilated renal pelvis. However, there were no treatment-related or statistically significant differences between treatment and control groups. All visceral variations observed were either random and sporadic or occurred at incidences within the range for historical controls.

TABLE 5: Summary of fetal visceral malformations/variations

Observations	Dose in mg/kg/day			
	0	20	60	180
Examined #Fetuses (#Litters)	107 (15)	102 (15)	96 (15)	103 (15)
Visceral malformations #Fetuses (#litters) Hernia diaphragmatica	0 (0) 0 (0)	0 (0) 0 (0)	0 (0) 0 (0)	1 (1) 1 (1)
Visceral variationsExternal variations #Fetuses (#litters) Separated origin of carotids Heart: traces of interventricular foramen/septum membranaceum Hypoplasia of gallbladder Dilated renal pelvis	13 (8) 9 (5) 3 (3) 1 (1) 0 (0)	16 (10) 10 (6) 6 (6) 0 (0) 0 (0)	10 (6) 5 (4) 5 (4) 1 (1) 0 (0)	18 (11) 13 (7) 4 (3) 0 (0) 1 (1)

Data taken from Tables 021-024, pp. 75-78, MRID 44496404.

3. Skeletal examination

The results of skeletal examination are shown in Table 6.The low incidence of fetal malformations observed for all treatment groups were within the range for historical controls and were not considered treatment- or dose-related. The random and sporadic skeletal malformations observed were fused, irregular, or absent cervical/thoracic/lumbar vertebra; cleft sternum; or deformed hyoid bone of the skull. Skeletal variations occurred randomly in all treatment groups. Variations observed were of the skull (splitting of skull bones, epactal bone between nasal and frontal or between frontal and parietal bones), the ribs (accessory 13th, shortened or absent 12th, or rudimentary cervical ribs), the vertebral column (accessory thoracic vertebra), deformed clavicula, and sternebra (irregular, fused, or accessory). Retardation of ossification was found in 52-67 % of fetuses and 87-100% of litters with no statistically significant or treatment-related differences observed between treatment groups and controls. Skeletal retardations observed included incomplete or missing ossification of the skull bones, vertebral column, sternebrae, metacarpal bones, and talus.

TABLE 6: Summary of fetal skeletal malformations/variations/retardations (ossification)

Observations	Dose in mg/kg/day			
	0	20	60	180
Examined #Fetuses (#Litters)	107 (15)	102 (15)	96 (15)	103 (15)
Skeletal malformations				
#Fetuses (#litters)	3 (3)	2 (2)	1 (1)	2 (2)
Hyoid bone deformed	0 (0)	0 (0)	1 (1)	0 (0)
Vertebrae fused &/or irregular shaped	0 (0)	0 (0)	0 (0)	1 (1)
Cervical vertebra absent	1 (1)	0 (0)	0 (0)	0 (0)
Thoracic vertebra absent	0 (0)	1 (1)	0 (0)	0 (0)
Lumbar vertebra absent	1 (1)	1 (1)	0 (0)	0 (0)
Lumbar vert. fused &/or irregular	1 (1)	0 (0)	0 (0)	0 (0)
Cleft sternum	0 (0)	0 (0)	0 (0)	1 (1)
Skeletal variations				
#Fetuses (#litters)	14 (8)	10 (6)	9 (7)	12 (9)
Splitting of skull bone(s)	1 (1)	0 (0)	2 (2)	0 (0)
Epactal between nasal and frontal	2 (2)	0 (0)	0 (0)	0 (0)
Epactal between frontal and parietal	0 (0)	1 (1)	1 (1)	0 (0)
Accessory thoracic vertebra	1 (1)	0 (0)	0 (0)	1 (1)
Clavicula deformed	0 (0)	0 (0)	1 (1)	0 (0)
Sternebrae fused	6 (4)	4 (3)	2 (2)	7 (5)
Sternebrae of irregular shape	2 (2)	0 (0)	1 (1)	2 (2)
Accessory sternebra	0 (0)	0 (0)	3 (2)	0 (0)
Accessory 13th rib (s)	5 (3)	4 (3)	1 (1)	5 (4)
12th rib (s) shortened	1 (1)	1 (1)	0 (0)	0 (0)
Rudimentary cervical rib (s)	0 (0)	0 (0)	0 (0)	2 (2)
12 th rib (s) absent	0 (0)	1 (1)	0 (0)	0 (0)
Skeletal retardations (ossification)				
#Fetuses (#litters)	67 (15)	61 (15)	56 (13)	52 (14)
Interparietal &/or parietal inc. oss.	0 (0)	0 (0)	1 (1)	0 (0)
Hyoid bone incompletely ossified	1 (1)	1 (1)	0 (0)	1 (1)
Skull incompletely ossified	0 (0)	1 (1)	1 (1)	2 (2)
Cervical vert. body/bodies inc. oss.	1 (1)	0 (0)	2 (2)	2 (2)
Thor. vert body/bodies inc. dumb. sh.	1 (1)	0 (0)	0 (0)	1 (1)
Lumbar vertebral arch (es) inc. oss.	13 (8)	7 (4)	8 (5)	4 (4)
Sacral vertebral arch (es) inc oss.	0 (0)	0 (0)	0 (0)	1 (1)
Sternebrae not ossified	24 (12)	21 (9)	24 (12)	17 (7)
Sternebrae inc. oss. or reduced size	36 (13)	34 (12)	31 (13)	32 (13)
Metacarpal bones inc. oss.	0 (0)	0 (0)	0 (0)	1 (1)
Talus incompletely ossified	0 (0)	0 (0)	0 (0)	1 (1)

Data taken from Tables 027-040, pp. 81-94, MRID 44496404.

III. DISCUSSION

A. INVESTIGATOR'S CONCLUSIONS

No deaths or abortions occurred in any treatment group. No statistically significant. ($p \leq 0.05$) or treatment-related clinical signs of maternal toxicity were observed at any dose level compared to controls. At 180 mg/kg/day, body weight gain was reduced 91% during the treatment period with a concurrent decrease (13.3%) in food consumption during the same period. No treatment-related maternal effects were observed at 20 or 60 mg/kg/day. There were no overt signs of developmental toxicity at any treatment level compared to controls.

Under the conditions of the study, the maternal LOAEL was 180 mg/kg/day and the maternal NOAEL was 60 mg/kg/day. The developmental LOAEL was not determined and the NOAEL was ≥180 mg/kg/day.

B. REVIEWER'S DISCUSSION

1. MATERNAL TOXICITY

No mortality, abortions, or clinical signs of toxicity occurred in any treatment group. There were no statistically or biologically significant gross necropsy observations at maternal sacrifice. There were no statistically significant differences in mean absolute body weights between the treated groups and the control group during the gestational period. At the 180 mg/kg/day dose level, there was a statistically significant ($p \leq 0.05$) decrease (57.0%) in body weight gain during GD 14-16 and a 91% (n.s.) reduction in body weight gain over the treatment period (GD 7-19) that was considered treatment-related. There was almost complete recovery in reduced body weight during the post-treatment period (GD 19- 29). There were no statistically significant or treatment-related changes in absolute or relative body weight at 20 or 60 mg/kg/day. Reduced food consumption correlated with the observed reduction in body weight gain at 180 mg/kg/day. Mean food consumption was reduced 16.6% on GD 10-11 and 19.9% on GD 12-13 and 13.3% overall during the treatment period. During the post-treatment period (GD 19-29) there was an 11.7% (n.s.) increase in food consumption compared to controls which corresponded to the recovery in body weight gain seen during this period and for the overall gestational period as well (GD 0-29). No treatment-related maternal changes in food consumption were noted at 20 or 60 mg/kg/day.

Therefore, based on reduction in mean body weight and food consumption during the treatment period, the maternal toxicity LOAEL is 180 mg/kg/day and the maternal toxicity NOAEL is 60 mg/kg/day.

2. DEVELOPMENTAL TOXICITY

a. Deaths/resorptions

Treatment with Tepraloxydim did not cause an increase in the number of dead fetuses or changes in total corpora lutea, implantation sites, resorptions/dam, and preimplantation or postimplantation losses.

b. Altered growth

No statistically significant or treatment-related differences in gravid uterine weight, fetal weights, or mean placental weights of viable fetuses were observed at any treatment level compared to controls. No significantly delayed maturation of fetuses was observed at any treatment level.

c. Developmental variations

Although a range of visceral and skeletal variations was observed, there were no biologically or statistically significant differences between treatment and control fetuses. All visceral and skeletal variations observed were either random and sporadic or occurred within the range for historical controls.

d. Malformations

The total fetal or litter incidence rates of visceral, external, or skeletal malformations were not statistically significantly ($p \leq 0.05$) increased at any treatment level.

Therefore, based on no observed adverse developmental effects, the developmental toxicity LOAEL is undetermined and the developmental toxicity NOAEL is ≥180 mg/kg/day.

C. STUDY DEFICIENCIES

No major deficiencies were identified in the conduct of this study.

D. CLASSIFICATION

This study is classified as **Acceptable/Guideline** and satisfies the guideline requirement for a developmental toxicity study in rabbits **(83-3b)**.