(10-30-00)

DATA EVALUATION REPORT

TRITICONAZOLE

Study Type: DEVELOPMENTAL – RABBIT
[OPPTS 870.3700 (§83-3b)]
MRID 44802106

Prepared for

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

Prepared by

Chemical Hazard Evaluation Group
Toxicology and Risk Analysis Section
Life Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37831
Task Order No. 00-17O

Primary Reviewer:
William J. Spangler, Ph.D.

Secondary Reviewer:
Carol S. Forsyth, Ph.D., D.A.B.T.

Group Leader
Robert H. Ross, M.S.

Quality Assurance:
Lee Ann Wilson, M.A.

Signature: Robert H. Ross for W. J. Spangler
Date: JUN 0 6 2000

Signature: Carol S. Forsyth
Date: JUN 0 6 2000

Signature: Robert H. Ross
Date: JUN 0 6 2000

Signature: L. A. Wilson
Date: JUN 0 6 2000

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This review may have been altered subsequent to the contractor's signatures above.

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TRITICONAZOLE **Developmental Toxicity Study [OPTS 870.3700 (§83-3b)]**

EPA Reviewers: William Greear, M.P.H., D.A.B.T. William Greear Date: 10-25-00
Registration Action Branch 3/HED (7509C)
EPA Work Assignment Manager: M. Copley, D.V.M., D.A.B.T. Marion Copley Date: 10/30/00
Registration Action Branch 1/HED (7509C)

DATA EVALUATION RECORD

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

DP BARKED: D261924
P.C. CODE: 125620

SUBMISSION CODE: S568827
TOX. CHEM. NO.: None

TEST MATERIAL (PURITY): RPA400727 (99.5% a.i.)

SYNONYMS: Triticonazole; 2-(4-chlorobenzilidine)-5,5-dimethyl-1-(1,2,4-triazolylmethyl)-1-cyclopentanol

CITATION: Burns, L.M. (1991) RPA400727: Teratology study in the rabbit. Life Science Research Limited, Eye, Suffolk IP23 7PX, England. LSR Report No. 91/RHA428/0916, November 28, 1991. MRID 44802106. Unpublished.

SPONSOR: Rhône-Poulenc Agrochimie, 14-20, rue Pierre Baizet, Boite Postale 9163, F-69263 Lyon Cedex 09, France

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 44802106), 20 presumed pregnant New Zealand White rabbits per group were administered RPA400727 (99.5% a.i., Lot #YG2156/1) by gavage at doses of 0, 5, 25, 50, and 75 mg/kg/day on gestation days (GD) 6-19, inclusive. The controls were given vehicle (0.5% aqueous methylcellulose mucilage) 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. At sacrifice, the neck and abdominal and thoracic cavities were examined for visceral malformations/variations. Following evisceration, approximately one-third of the fetal heads were fixed in Bouin's fluid and free-hand sectioned. The remaining torsos and fetuses were fixed in denatured alcohol, further processed, stained, and examined for skeletal malformations/variations and ossification.

No treatment-related deaths, clinical signs, or effects on body weight change or food consumption were observed in the 5 or 25 mg/kg/day groups. Six does in the 75 mg/kg/day group and one in the 50 mg/kg/day group were sacrificed *in extremis* following the observations of extreme weight loss, reduced food intake, reduced fecal output, reduced body temperature, increased respiration rate, and red staining in the cage undertray. Body weight gain by the 50 and 75 mg/kg/day group was significantly ($p \leq 0.001$) less than the controls during GD 6-8. Food consumption during the treatment interval by the 50 and 75 mg/kg/day animals was 82-81% and

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65-88%, respectively, of the control levels. No treatment-related lesions were found in any animal at necropsy.

Therefore, the maternal toxicity LOAEL is 50 mg/kg/day based on decreased body weight gain after dosing initiation, reduced food consumption, and mortality, and the maternal toxicity NOAEL is 25 mg/kg/day.

One high-dose doe aborted on GD 19 following extreme weight loss and clinical signs of toxicity. No significant differences were observed in pregnancy rate, mean numbers of corpora lutea and implantation sites, viable fetuses, fetal weights, fetal sex ratios, or placental weights of the treated groups as compared with the control group. Pre- and post-implantation losses by the high-dose group were 28.8% and 20.7%, respectively, compared with 18.9% and 13.6%, respectively, for the control group.

No treatment-related increased incidences of external or visceral malformations/variations were observed in any group as compared with the controls. In the high-dose group, slight (n.s.) increases in the percent of fetuses with variations in midline cranial sutures were observed: forward extended anterior fontanelle occurred in 4.8% of fetuses (3 litters) and irregular ossification of the frontal suture was observed in 17.5% of fetuses (8 litters) compared with 0.8% (1 litter) and 5.6% (5 litters), respectively, in the controls.

Therefore, the developmental toxicity LOAEL is 75 mg/kg/day based on cranial variations, abortion, and increased pre- and post-implantation losses. The developmental toxicity NOAEL is 50 mg/kg/day.

This study is classified as **Acceptable/Guideline** and satisfies the guideline requirements for a developmental toxicity study in rats **[OPPTS 870.3700 (§83-3b)]**.

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

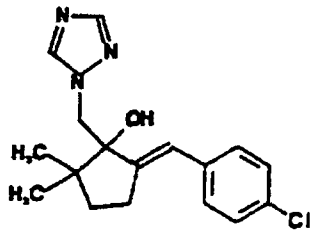
I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: RPA400727

   Description: white powder
   Lot No.: YG2156/1
   Purity: 99.5% a.i.
   Stability of compound: proven by reanalysis
   Other: stored in dark at 4°C
   CAS No.: not provided

Structure:



2. Vehicle and/or positive control

Aqueous methylcellulose mucilage (0.5% aqueous solution; w/v) was used as the vehicle and negative control. No positive control was used in this study.

3. Test animals

Species: rabbit
Strain: New Zealand White
Age and weight at study initiation: ≈19-27 weeks; 3.51-4.85 kg weight on GD 0
Source: Froxfield SPF Rabbits Limited, Broadway Farm, Froxfield , Hampshire, England
Housing: Animals were housed individually in suspended stainless steel cages with perforated floor panels
Diet: SQC standard rabbit diet (Special Diet Services Limited, Witham, Essex, England) was available *ad libitum*.
Water: Tap water was available *ad libitum*.
Environmental conditions:
Temperature: 15-23 °C
Humidity: 40-70%
Air changes: 17-20/hour
Photoperiod: 14-hour light/10-hour dark
Acclimation period: ≥7 days

B. PROCEDURES AND STUDY DESIGN

This study was designed to assess the developmental toxicity potential of RPA400727 when administered by gavage to rabbits on GD 6-19, inclusive.

1. In life dates

Start: January 16, 1991; end: February 28, 1991

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2. Mating

Two weeks prior to shipment, the supplier synchronized ovulation in does by i.v. injection of lutenizing hormone. After acclimation, groups of 20 virgin female New Zealand White rabbits were inseminated with pooled semen from males of the same strain. Following insemination, ovulation was induced by i.v. injection of each doe with lutenizing hormone. The day of insemination was designated GD 0.

3. Animal assignment

Animal assignment and dose selection is presented in Table 1. Assignment of mated animals was randomized by evenly distributing does inseminated on any one day among the 5 treatment groups.

TABLE 1. Animal assignment

Treatment Group	Dose (mg/kg/day)	Number Assigned
Control	0	20
Low Dose	5	20
Low Mid Dose	25	20
High Mid Dose	50	20
High Dose	75	20

Data taken from page 15, MRID 44802106.

4. Dose selection rationale

Doses were based on the results of a preliminary study (LSR Report No. 90/RHA346/0848). Details of this study were not included in the main report.

5. Dosing

All doses were administered in a volume of 5.0 mL/kg of body weight/day. Daily dose volumes were based on individual body weights recorded prior to each dosing period.

6. Dose solution preparation and analysis

Dosing solutions were prepared separately in 0.5% aqueous carboxymethyl cellulose (w/v) to give nominal concentrations of 1.0, 5.0, 10.0, or 15.0 mg/mL. The dosing solutions were prepared fresh daily and homogeneity during dosing was maintained by constant stirring on a magnetic stirrer. The data submitted for determining the 48-hour stability (0, 24, and 48 hours) of RPA 400727 at 21 °C was obtained from a

previous study (RHA/373/RPA400727). Homogeneity data obtained by analysis of samples taken at six equidistant depths throughout the dosing container for dosing solutions at 1 and 100 mg/mL were derived from the same study. Concentration was analyzed for the current study using samples of each dosing solution taken during the first and last weeks of treatment.

Results

Stability analysis: Samples taken for stability analysis at 0, 24, and 48 hours after preparation yielded mean respective values of 92.8, 94.6, and 93.0% of initial concentration for a 1.0 mg/mL solution and 95.6, 102.5, and 105.0% of initial concentration for a 100 mg/mL solution; within the ±10% allowable range.

Homogeneity analysis: Samples taken for homogeneity were 86.8-96.7% of nominal at 1.0 mg/mL, and 92.5-101.0% of nominal at 100 mg/mL.

Concentration analysis: The mean actual concentrations of the 1.0, 5.0, 10.0, and 15.0 mg/mL dosing suspensions, ranged from 97.6-105.0% of nominal for the first week of treatment and 98.6-105.2% of nominal for the final week of treatment; within the allowable limit of ±10%.

The analytical data indicated that the dosing solutions were stable for 48 hours at ambient temperature (21 °C) and that the variance between nominal and actual dosage to the study animals was acceptable.

C. OBSERVATIONS

1. Maternal observations and evaluations

All animals were weighed daily and observed for clinical signs of toxicity and mortality. Does found moribund were sacrificed and subjected to necropsy and examination of the visceral organs. Animals that aborted were sacrificed and the numbers of corpora lutea and implantation sites were noted. When possible, fetuses were examined. Maternal body weight changes per se were not calculated from absolute body weight data. Food consumption was recorded during GD 1-5, 6-12, 13-19, 20-23, and 24-28. On GD 29 does were sacrificed by i.v. injection of sodium pentobarbitone and cesarean sections were performed as well as gross pathology of the thoracic and abdominal cavities. The uteri and ovaries were removed; ovaries were examined for numbers of corpora lutea and uteri were examined for total implantation sites and live, dead, and resorbed fetuses. In cases where pregnancy was questionable, uteri were checked for implantation sites using a staining technique. Placental weights were recorded. Conception rates and preimplantation and post-implantation losses were calculated for each treatment group.

2. Fetal evaluations

All fetuses were sexed, weighed, and sacrificed by pentobarbitone sodium injection, then examined for external malformations/variations. The neck and thoracic and abdominal cavities were examined for visceral malformations/variations. All fetuses were then eviscerated. Approximately one-third of the fetuses per litter were decapitated and the heads fixed in Bouin's fluid for free-hand sectioning and examination. The remaining fetuses and torsos were fixed in denatured alcohol. The fetuses fixed in ethanol were further processed and stained by a modified method of Dawson, then examined for skeletal malformations and variations.

D. DATA ANALYSIS

1. Statistical analysis

Means and standard deviations were calculated where appropriate. Data for body weight gain were analyzed by analysis of variance (ANOVA) and compared to controls using the Williams test. The incidence of fetal abnormalities per litter were analyzed using a generalized linear model (GLM) with binomial distribution and a non-zero variance scale factor was estimated using the Pearson chi-squared statistic. Pairwise contrasts with controls were performed. The level of significance was set at a confidence interval of 95, 99 or 99.9% ($p \leq 0.05$, 0.01, or 0.001).

2. Historical control data

Data were provided to allow comparison with concurrent controls.

II. RESULTS

A. MATERNAL TOXICITY

1. Mortality and clinical signs

Nine deaths occurred during the study. Six does in the 75 mg/kg/day treatment group and one doe in the 50 mg/kg/day treatment group were killed *in extremis* during GD 13-17 after severe weight loss; one doe each was killed *in extremis* at 5 and 50 mg/kg/day because of intubation accidents. Deaths due to sacrifice following severe weight loss at 50 and 75 mg/kg/day were considered treatment-related. Clinical signs of toxicity in animals sacrificed following weight loss included reduced food intake, reduced fecal output, reduced body temperature, increased respiration rate, and red staining in cage undertrays. No treatment-related deaths or clinical signs of toxicity were observed in controls or in the 5 and 25 mg/kg/day treatment groups.

2. Body weight

Selected body weight data are listed in Table 2. Absolute body weights were not analyzed statistically. Weight gain by the 50- and 75-mg/kg/day groups was significantly ($p \leq 0.001$) less than the controls during GD 6-8 which resulted in slightly reduced absolute body weights for these animals throughout the dosing interval. Recovery was complete in surviving 50 and 75 mg/kg/day does during the post-treatment period. Relative body weight gain was not calculated for this study. There were no statistically significant or treatment-related differences in body weight changes at 5 or 25 mg/kg/day, compared to controls.

TABLE 2: Selected maternal body weights and food consumption during gestation

Gestation Day	Dose in mg/kg/day (# of does)				
	0 (20)	5 (16)	25 (18)	50 (16)	75 (13)
Mean body weight (kg)					
0	4.05±0.27	4.02±0.36	3.93±0.23	4.06±0.24	4.11±0.35
6	4.11±0.23	4.09±0.35	4.03±0.24	4.18±0.28	4.23±0.32
8	4.12±0.25	4.11±0.34	4.00±0.25	4.10±0.27***	4.07±0.33***
10	4.16±0.25	4.13±0.34	4.05±0.23	4.15±0.30	4.08±0.33
12	4.18±0.25	4.18±0.34	4.07±0.24	4.18±0.30	4.14±0.30
14	4.23±0.27	4.23±0.34	4.14±0.26	4.20±0.30	4.20±0.31
16	4.27±0.26	4.27±0.33	4.18±0.26	4.23±0.29	4.25±0.32
18	4.30±0.27	4.29±0.35	4.21±0.27	4.26±0.27	4.23±0.34
20	4.30±0.27	4.26±0.35	4.22±0.27	4.26±.30	4.26±0.35
24	4.37±0.28	4.36±0.32	4.27±0.25	4.35±0.29	4.36±0.30
28	4.41±0.26	4.42±0.26	4.33±0.25	4.41±0.29	4.43±0.28
Mean food intake (g/animal/day)					
1-5	176±20	188±23	183±32	179±26	189±30
6-12	179±33	174±22	157±28	147±34 (82)[a]	117±39 (65)
13-19	172±33	158±34	160±44	139±51 (81)	151±61 (88)
20-23	143±43	132±29	131±43	152±54 (106)	180±37 (126)
24-28	115±39	95±38	102±36	114±37 (99)	141±42 (123)

Data taken from Tables 3 and 4, pp 26 and 27; MRID 44802106.
[a]Number in parentheses is percent of control; calculated by reviewer.
***Body weight change with respect to GD 6 statistically significantly different from control; $p \leq 0.001$.

3. Food consumption

Food consumption is summarized in Table 2. Food consumption data were not analyzed statistically. During the treatment period, food consumption by the 50- and 75-mg/kg/day groups was 81-82% and 65-88%, respectively, of the control levels. There was a rebound in food consumption at 50 and 75 mg/kg/day during the post-treatment period. At 5 and 25 mg/kg/day, slightly lower food consumption as compared with the controls was not considered biologically significant or treatment related.

4. Gross pathology

There were no 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. Four does had complete litter loss: one each at 5 and 75 mg/kg/day aborted and two at 25 mg/kg/day had whole litter resorption. While abortion is not uncommon in rabbits, abortion by the high-dose animal on GD 19 was associated with extreme weight loss and clinical signs, and was, therefore, considered treatment-related. A slight, but not statistically significant increase in pre- and post-implantation losses were observed at 75 mg/kg/day. There were no statistically significant or treatment-related differences in pregnancy rate, mean number of corpora lutea and implantation sites, viable fetuses, fetal weights, and sex ratios. Likewise no statistically significant or treatment-related differences were observed in the placental weight of fetuses at any dose level compared to controls.

TABLE 3. Cesarean section observations in rabbits

Observations	Dose in mg/kg/day				
	0	5	25	50	75
No. Animals Assigned	20	20	20	20	20
No. Animals Pregnant	20	18	20	18	20
Pregnancy Rate (%)[a]	100	90	100	90	100
Maternal Mortality	0	1	0	2	6
Delivered Early/Aborted	0	1	0	0	1
Total Litters Resorption	0	0	2	0	0
Total Corpora Lutea[a]	239	192	239	218	163
Corpora Lutea/Doe	12.7±2.2	12.8±2.1	12.1±2.7	13.6±2.9	12.5±2.3
Total Implantations[a]	206	186	200	179	116
Implantations/Doe	10.3±3.2	11.6±2.2	10.4±2.7	11.2±3.5	8.9±2.4
Preimplantation Loss (%)	18.9	9.7	14.2	17.9	28.8
Postimplantation Loss (%)	13.6	8.1	7.4	16.2	20.7
Total Resorptions/Doe	1.4±1.2	0.9±1.0	0.8±0.9	1.8±1.3	1.8±1.4
Early Resorptions	1.0±1.0	0.4±0.6	0.6±0.7	1.6±1.3	1.5±1.2
Late Resorptions	0.5±0.7	0.4±0.6	0.7±0.8	0.3±0.5	0.3±0.6
Dead Fetuses/Litter	0.0±0.0	0.2±0.4	0.1±0.3	0.0±0.0	0.0±0.0
Does with Viable Fetuses at Term	20	16	18	16	13
Total Live Fetuses[a]	169	147	174	150	92
Live Fetuses/Litter	8.9±2.7	10.7±2.1	9.7±2.9	9.4±3.9	7.1±3.0
Live Mean Fetal Weight (g)	39.8±2.1	39.8±1.5	39.4±1.4	39.1±1.6	39.7±2.7
Live Weight/Male Fetus (g)	40.7±2.5	40.0±1.9	39.3±1.8	39.5±2.2	40.5±2.4
Live Weight/Female Fetus (g)	36.3±2.8	39.3±2.4	39.3±2.0	37.9±3.0	39.4±2.5
Sex Ratio (% Male)[a]	58.4	57.3	55.4	51.3	50.0
Mean placental weight of fetuses (g)	5.1±0.3	5.1±0.2	5.3±0.2	5.2±0.2	5.2±0.3

Data taken from Tables 1, 5, and 6, and Appendix 6, pp. 24, 28, and 29, and 67-71, respectively, MRID 44802106.
[a]Calculated by reviewer.

B. DEVELOPMENTAL TOXICITY

There were no statistically significant ($p \leq 0.05$) or treatment-related external, visceral, or skeletal malformations in the fetuses at any dose level. The findings for external and visceral, head, and skeletal examinations for variations and ossification are summarized in Tables 4, 5, and 6, respectively. These data were presented in the report as percent of fetuses/group and total number of litters/group affected.

1. External examination

The results of external examination are shown in Table 4. There were no statistically significant ($p \leq 0.05$) increased incidences of external malformations or variations at any dose level. At 75 mg/kg/day, 3.3% of the total fetuses showed reduced, vestigial, or rudimentary tails compared to 0.0% in controls. Fetuses were randomly affected in two litters. Although no historical control data were available for this parameter, this observation was not statistically significantly increased and was not considered to be treatment related. No other elevated incidence of external malformations or variations was observed at any treatment level.

2. Visceral examination

The results of visceral examination are shown in Table 4. No statistically significant incidence of visceral malformations were observed in any treatment group, compared to controls. At 75 mg/kg/day, 4.3% of fetuses (distributed in 3 litters) exhibited a visceral variation in the form of dark, red, or reduced stomach contents. Although the incidence observed was slightly higher than the upper range for historical controls (0-2.7% of fetuses), this observation was not considered biologically significant or treatment-related. No other elevated incidences of visceral malformations or variations were observed at any treatment level.

TABLE 4: Findings of external and visceral examination of fetuses

Observations	Dose in mg/kg/day				
	0	5	25	50	75
Number of fetuses (#litters) examined	178 (20)	171 (16)	174 (18)	150 (16)	92 (13)
External variations Tail reduced/vestigial/rudimentary	0.6 (1)[a]	0.6 (1)	0.0 (0)	0.0 (0)	3.3 (2)
Visceral variations Stomach contents dark/red/reduced	0.0 (0)	0.6 (1)	0.0 (0)	0.7 (1)	4.3 (3)

Data taken from Table 7, pp. 31-32; MRID 44802106.
[a]% of fetal incidence (# litters)

3. Skeletal examination

The results of skeletal examination of free-hand sectioned heads are shown in Table 5 and for the full skeleton in Table 6. A variety of skeletal variations and changes in ossification were found in free-hand sectioned heads that are known to be random and sporadic in the strain of rabbit used in this study. For the 75 mg/kg/day treatment group, only the parameters shown in Table 5 occurred at incidences higher than those for historical controls although statistical significance was not attained in the current study. The most pronounced effects were the increased incidences of forward extended anterior fontanelle and irregular ossification of the frontal suture. No statistically significant or treatment-related malformations, variations or differences in ossification rates were observed in the heads of 5, 25, or 50 mg/kg/day fetuses. Findings of full skeletal examination of fetuses indicate only a statistically significantly ($p \leq 0.05$) increased incidence of precocious ossification of the acromion process of the scapula (i.e., elongation; 10.9% of fetuses distributed within 4/13 litters) in the 75 mg/kg/day fetuses as compared with controls. No other statistically significantly increased or treatment-related incidences of malformations, variations or changes in ossification rate were observed for the 5, 25, or 50 mg/kg/day treatment groups, compared to controls.

TABLE 5: Findings of skeletal examination of fetal heads

Observations	Dose in mg/kg/day				
	0	5	25	50	75
Number of fetuses (#litters) examined	124 (20)	118 (16)	121 (18)	103 (15)	63 (13)
Variations					
Anterior fontanelle extended anterio	0.8 (1)[a]	0.0 (0)	0.0 (0)	1.0 (1)	6.3 (2)
Lachrymal fossa enlarged	0.8 (1)	0.0 (0)	0.0 (0)	1.0 (1)	4.8 (3)
Minor cranial anomalies	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	1.6 (1)
Ossification					
Additional suture in parietal bone	0.8 (1)	0.0 (0)	0.0 (0)	1.0 (1)	3.2 (1)
Irregular oss. of frontal suture	5.6 (5)	2.5 (3)	1.7 (2)	5.8 (4)	17.5 (8)
Additional plaque in nasal suture	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	6.3 (4)
Frontal suture enlarged at fronto-nasal junction	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	3.2 (1)

Data taken from Table 8, pp. 34-36; MRID 44802106.
[a]% of fetal incidence (#litters).

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TABLE 6: Findings of full skeletal examination of fetuses					
Observations	Dose in mg/kg/day				
	0	5	25	50	75
Number of fetuses (#litters) examined	178 (20)	171 (16)	174 (18)	150 (16)	92 (13)
Skeletal variations					
Xiphisternum bifurcated	0.6 (1)[a]	0.0 (0)	0.0 (0)	0.7 (1)	1.1 (1)
Rudimentary floating 13th rib (s)	3.9 (5)	2.3 (3)	6.3 (9)	3.3 (5)	10.9 (6)
Skeletal ossification					
Two or more caudal vertebrae fused	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	2.2 (2)
Inc. oss. of heads of limb long-bones	66.3 (19)	58.5 (15)	65.5 (16)	76.0 (14)	84.8 (13)
Acromion process (es) elongated	1.7 (1)	0.0 (0)	3.4 (4)	5.3 (5)	10.9 (4)*
Inc. oss. of one or more thoracic vertebral centra	0.0 (0)	0.0 (0)	0.0 (0)	0.7 (1)	2.2 (1)

Data taken from Table 8, pp. 37-41; MRID 44302106.
[a]% of fetal incidence (#litters).
*Statistically significantly different from control; $p \leq 0.05$.

III. DISCUSSION

A. INVESTIGATOR'S CONCLUSIONS

The study author concluded that once-daily oral administration of RPA400727 to pregnant rabbits during the period of major organogenesis was associated with a dose-related incidence of mortality, transient weight loss, and reduced food consumption during the first few days of treatment at 50 and 75 mg/kg/day. Fetal observations at 75 mg/kg/day included slightly higher incidences of pre- and post-implantation losses and increases in the incidence or minor skeletal abnormalities involving anterior cranial bones and the scapula. The maternal NOAEL was considered to be 25 mg/kg/day and the fetal developmental NOAEL was 50 mg/kg/day.

B. REVIEWER'S DISCUSSION

1. MATERNAL TOXICITY

Maternal deaths in the 50 and 75 mg/kg/day groups associated with severe weight loss and clinical signs of toxicity were considered treatment-related. Deaths resulting from intubation errors were incidental to treatment. Decreased food consumption by the 50 and 75 mg/kg/day animals corresponded with weight loss at the beginning of the treatment period. Recovery of both weight gain and food consumption occurred post-dosing.

Therefore, the maternal toxicity LOAEL is 50 mg/kg/day based on decreased body weight gain after dosing initiation, reduced food consumption, and mortality, and the maternal toxicity NOAEL is 25 mg/kg/day.

2. DEVELOPMENTAL TOXICITY

a. Deaths/resorptions

Treatment with RPA 400727 did not cause a treatment- or dose-related increase in the number of dead fetuses or changes in numbers of corpora lutea, implantation sites or resorptions/dam. However, at 75 mg/kg/day, abortion in one dam and the slightly increased pre- and post-implantation losses correlated with pronounced maternal toxicity and are considered treatment-related.

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. Enhanced ossification of the scapula is not considered adverse and the relationship to treatment is unknown.

c. Developmental variations

No differences in external or visceral variations were observed in any treatment group compared to controls. Although a range of visceral and skeletal (excluding cranium) variations were observed, there were no biologically or statistically significant differences between treatment and control fetuses. All visceral and skeletal variation occurrences were either random and sporadic, not dose-related, or occurred within the range for historical controls. Variations in midline cranial sutures, involving mainly bones of the anterior cranium, were slightly increased in fetuses from the high-dose does as compared with both the concurrent and historical controls. The biological significance of this is unknown, but may have been a result of maternal toxicity.

d. Malformations

No external, visceral, or skeletal malformations were observed in any treatment group.

Therefore, the developmental toxicity LOAEL is 75 mg/kg/day based on cranial variations, abortion, and increased pre- and post-implantation losses. The developmental toxicity NOAEL is 50 mg/kg/day.

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C. STUDY DEFICIENCIES

No deficiencies were noted 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 rats **[OPPTS 870.3700 (§83-3b)]**.