(11-15-00)

DATA EVALUATION REPORT

TRITICONAZOLE

Study Type: DEVELOPMENTAL – RAT (83-3A)
[OPPTS 870.3700 (§83-3)]
MRIDs 44802104, 44802105

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. 00-17N

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

Signature: Robert N. Ross for W.J. Spangler
Date: MAR 1 2 2000

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

Signature: Carol S. Forsyth
Date: MAR 1 2 2000

Group Leader
Robert H. Ross, M.S.

Signature: Robert N. Ross
Date: MAR 1 2 2000

Quality Assurance:
Lee Ann Wilson, M.A.

Signature: L. A. Wilson
Date: MAR 1 2 2000

Disclaimer

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

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EPA Reviewer: Unassigned Stanley B. Gross RAB 3 Date: 11/1/2000

EPA Work Assignment Manager: M. Copley, D.V.M., D.A.B.T. Date: 11/15/2000
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DATA EVALUATION RECORD

STUDY TYPE: Developmental Toxicity - Rat;OPPTS 870.3700 [§83-3a]

DP BARCODE: 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 rat. Life Science Research Limited, Eye, Suffolk, IP23 7PX, England. LSR Report No. 90/RHA373/0189, April 10, 1991. MRID 44802105. Unpublished.

Higgins, C. (1990) RPA400727: Preliminary teratology study in the rat. Life Science Research Limited, Eye, Suffolk, IP23 7PX, England. LSR Report No. 90/RHA324/0428, May 21, 1990. MRID 44802104. Unpublished.

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

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 44802105), 25 presumed pregnant Sprague Dawley (CD) rats per group were administered RPA400727 (99.5% a.i.) by gavage at doses of 0, 40, 200, and 1000 mg/kg/day on gestation days (GD) 6-15, inclusive. The controls were given vehicle (0.5% w/v aqueous methylcellulose mucilage) only for the same dosing period. Doses for this study were selected on the basis of a rangefinding study (MRID 44802104) in rats. On GD 20, all dams 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. Approximately one-half of the fetuses were eviscerated and fixed in denatured ethanol and the remainder were placed in Bouin's fixative and examined for visceral malformations/variations. The ethanol-fixed fetuses were further processed, stained with Alizarin-red, and examined for skeletal malformations/variations and differences in ossification rates.

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. Food consumption was marginally reduced (5.4-8.3%) throughout the treatment and post-treatment periods at 1000 mg/kg/day, but was not statistically significantly

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different from controls. At the 1,000 mg/kg/day dose level, there was also a marginal reduction in mean body weight (1.9-4.1%) during the treatment and post-treatment periods (GD 6-19) and a statistically significant reduction in mean body weight gain ($p \leq 0.05$; 14.5%) during GD 12-16. No treatment-related maternal changes were noted at 40 or 200 mg/kg/day.

Therefore, based on reduction in mean body weight gain from GD 12-16, the maternal toxicity LOAEL is 1000 mg/kg/day and the maternal toxicity NOAEL is 200 mg/kg/day.

Treatment with RPA400727 did not cause any statistically significant or treatment-related changes in gestational or cesarean section parameters at any treatment level. At 1,000 mg/kg/day, increased incidences of unilateral supernumerary ribs (16.9% of fetuses and 15/23 litters vs. 11.7% of fetuses and 11/24 litters in controls) and bilateral supernumerary ribs were observed (14.5% of fetuses and 9/23 litters vs. 5.0% of fetuses and 5/24 litters in controls). Although not significantly different ($p \leq 0.05$) from controls, the incidences of these skeletal variations at 1,000 mg/kg/day were greater than the upper limits for historical controls and were considered treatment-related. No statistically significant or treatment-related differences in external malformations/variations, visceral malformations/variations, or skeletal malformations/ossification reductions were observed in fetuses at any treatment level including controls.

Therefore, based on a treatment-related increases in unilateral and bilateral supernumerary ribs, the developmental toxicity LOAEL is 1000 mg/kg/day and the developmental NOAEL is 200 mg/kg/day.

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

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: YG 2156/1
   Purity: 99.5% a.i.
   Stability of compound: measured by reanalysis at 6-month intervals and/or at the completion of the study
   CAS No.: not provided

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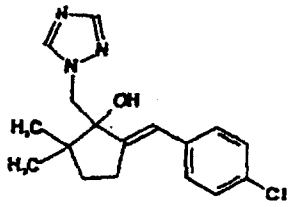
Structure:



2. Vehicle and/or positive control

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

3. Test animals

Species: rat
Strain: Sprague Dawley (CD)
Age and weight at study initiation: ≈9-11 weeks of age; 201-252 g on GD 0
Source: Charles River U.K. Limited, Margate, Kent, England
Housing: Animals were housed individually, in suspended polypropylene cages with stainless steel tops and meshed bottoms, except during mating (1:1) and acclimation (5 per cage).
Diet: Biosure, Laboratory Diet No. 1 (Biosure, Lavender Mill, Manea, Cambridgeshire, England) was available *ad libitum*.
Water: Tap water was available *ad libitum*.
Environmental conditions:
Temperature: 18-25°C
Humidity: 40-70%
Air changes: ≈15 per hour
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 RPA400727 when administered by gavage to rats on GD 6-15, inclusive.

1. In life dates

Start: June 12, 1990; end: July 5, 1990

2. Mating

Females were housed 1 per male during mating, then housed individually after mating was confirmed. Day 0 of gestation was confirmed by microscopic examination of

vaginal mucus for spermatozoa or after finding at least 3 copulatory plugs beneath cages on the morning following overnight cohabitation.

3. Animal assignment

Animal assignment and dose selection are presented in Table 1. Assignment of mated animals was sequential by group and cage position to ensure daily matings were evenly distributed among the treatment groups.

TABLE 1. Animal assignment

Treatment Group	Dose (mg/kg/day)	Number Assigned
Control	0	25
Low Dose	40	25
Mid Dose	200	25
High Dose	1000	25

Data taken from page 15, MRID 44802105.

4. Dose selection rationale

Doses were selected on the basis of a rangefinding study (MRID 44802104). Six Sprague Dawley (CD) rats per group were administered RPA400727 in 0.5% aqueous methylcellulose mucilage by gavage at 0, 50, 250, or 1250 mg/kg/day on GD 6-15, inclusive. Animal care, maintenance, dosing, and mating procedures were as described for the main study. Animals were observed daily for clinical signs of toxicity and mortality. Body weights were recorded on GD 0, 3, 6-16 inclusive, 18, and 20. Food and water consumption were recorded on GD 0, 3, 6, 9, 12, 16, 18, and 20. All animals were sacrificed on GD 20 by CO_2 asphyxiation. The dams were observed macroscopically for clinical signs of toxicity or anatomical changes, then opened for removal of the reproductive tract. The number of corpora lutea in each ovary was recorded before removal. The uterus of each dam was removed, opened, and examined for pregnancy, number and distribution of implantations, live and dead fetuses, and early and late resorptions. Fetuses were weighed, sexed, and observed for external abnormalities. Placental weights were recorded for each fetus. The neck and the abdominal and thoracic cavities of approximately two-thirds of each litter were examined, then fetuses were eviscerated, placed in denatured ethanol, and stored. The remaining fetuses were placed in Bouin's fixative and stored.

No maternal deaths were observed at any treatment level. Clinical signs of toxicity observed in three dams at 1250 mg/kg/day were brown head, body, or peri-genital staining beginning early in the treatment period. Body weight gain in dams was reduced at 1250 mg/kg/day, compared to controls, with post-treatment recovery. Inter-group variation in food and water consumption was observed at 50, 250, and

1250 mg/kg/day, but did not differ significantly from control values. No adverse effects were observed at necropsy for any treatment group.

Inter-group variation in the number of implantations, viable fetuses, resorptions and pre- and post-implantation losses were observed which were not considered treatment-related. Mean fetal weight was slightly reduced and placental weight slightly increased at 1250 mg/kg/day, but both observations were considered equivocal and not treatment-related. An equivocal dose-related increase in the incidence of hydronephrosis was observed in some litters and fetuses of the 50, 250, and 1250 mg/kg/day treatment groups compared to controls.

Based on these results, doses up to the limit dose (40, 200, and 1000 mg/kg/day) were fixed for the main study. Range-finding data were also included for another pesticide (LS840606). However the results were not relevant to data obtained for RPA400727 and were not included in this discussion.

5. Dosing

All doses were administered in a volume of 10.0 mL/kg of body weight/day on GD 6-15, inclusive. Daily doses were based on the individual body weights of dams on the day of dosing.

6. Dose solution preparation and analysis

Dosing solutions were prepared separately by suspending RPA400727 in 0.5% (w/v) aqueous methylcellulose to give nominal concentrations of 4.0, 20.0, or 100.0 mg/mL. The dosing solutions were prepared fresh daily and homogeneity during dosing was maintained by constant stirring on a magnetic stirrer. The 48-hour stability (0, 24, and 48 hours) of the test article at 4.0 and 100.0 mg/mL was determined prior to initiation of the experiment. Homogeneity was tested by analysis of samples taken at six equidistant depths throughout the dosing container for dosing solutions at 4.0 and 100.0 mg/mL. Concentration was analyzed from samples of each dosing solution taken during the first and last weeks of treatment.

Results

Stability analysis: Samples taken for stability analysis 0, 24, and 48 hours after preparation yielded mean respective values of 99.2, 97.8, and 98.3% of initial concentration at 4.0 mg/mL and 97.4, 100.2, and 101.7% of initial concentration at 100.0 mg/mL; within the ±10% allowable range.

Homogeneity analysis: Multiple samples from the 4 and 100 mg/mL solutions ranged from 94-111% and 92.5-101%, respectively, of nominal.

Concentration analysis: The mean actual concentrations of the 4.0, 20.0, and 100.0 mg/mL suspensions taken during the first and last weeks of dosing, ranged from 105.5-111.0% of nominal and varied only slightly from the allowable limit of ±10%.

The analytical data indicated that the dosing solutions were homogeneous, stable for 48 hours at ambient temperature, 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 observed daily for clinical signs of toxicity and mortality. Maternal body weights were recorded on GD 0, 3, 6-16 inclusive, 18, and 20 and body weight changes were calculated. Food consumption was recorded at 2-4 day intervals on GD 3, 6, 9, 12, 16, 18, and 20. On GD 20, dams were sacrificed by CO_2 asphyxiation and examined externally for macroscopic malformations/variations. 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 (before removal), and uteri were examined for total implantation sites and live, dead, and resorbed fetuses. Dams without obvious signs of pregnancy were checked for implantation sites using a staining technique. Conception rates and preimplantation and postimplantation losses were calculated for each treatment group.

2. Fetal evaluations

All fetuses were sexed, weighed, and examined for external malformations/variations. Placental weights and placental abnormalities were recorded. Approximately one-half of the fetuses per dam were eviscerated and fixed in denatured ethanol and the remainder were placed in Bouin's fixative and examined for visceral malformations/variations according to Wilson's free-hand sectioning technique. The fetuses fixed in ethanol were further processed and stained with Alizarin-red, by a modified method of Dawson, then examined for skeletal malformations/variations and differences in ossification rates.

D. DATA ANALYSIS

1. Statistical analysis

Data for maternal body weight changes were analyzed using analysis of variance (ANOVA) and comparisons to controls were made using William's test for ordered comparison. Fetal abnormalities were evaluated on a litter-basis using a generalized linear model with binomial distribution and non-zero variance 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% ($p \leq 0.05$).

2. Historical control data

Historical control 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. One control dam was found dead on GD 8 with no previous history of poor health. No clinical signs of toxicity were observed in any treatment group including controls.

2. Body weight

Selected body weight and body weight gain data are listed in Table 2. At 1000 mg/kg/day, absolute body weights were consistently reduced throughout the treatment and post-treatment periods (1.9-4.1%), but these values were not statistically significantly different ($p \leq 0.05$) from controls. However, at 1000 mg/kg/day there was a statistically significant ($p \leq 0.05$) decrease in mean weight gain (14.5%) during GD 12-16 that was considered treatment-related. There were no biologically significant differences in absolute body weight and change in body weight at 40 or 200 mg/kg/day, compared to controls.

3. Food consumption

Food consumption is summarized in Table 2. Notwithstanding a slight, consistent reduction in food consumption at 1000 mg/kg/day (5.4-8.3%), there were no statistically significant ($p \leq 0.05$) or dose-related differences in mean food consumption at any dose level for dams throughout the treatment and post-treatment periods as compared to controls.

4. Gross pathology

Two dams each at 200 and 1000 mg/kg/day showed pale areas on the median or lateral liver lobes at necropsy and 1, 1, and 3 dams had red/brown staining on the head/nose/ears at 40, 200 and 1000 mg/kg/day, respectively. These observations were not statistically significant ($p \leq 0.05$) or treatment-related.

TABLE 2: Selected maternal body weights, body weight gains, and food consumption during gestation				
Gestational day	**0 mg/kg/day**	**40 mg/kg/day**	**200 mg/kg/day**	**1000 mg/kg/day**
Mean body weight (g)				
0	226	227	228	225
3	253	257	257	252
6	270	273	272	265
8	284	287	285	277
10	300	302	301	292
12	318	321	319	309
14	337	339	337	326
16	363	362	359	348
18	397	397	394	381
20	437	439	434	419
Mean body weight gain (g)				
6-12	47.6	48.2	46.5	44.7
12-16	44.7	41.2	39.9	38.2*
Mean food intake (g/animal/day)				
0-2	25	26	26	25
3-5	27	28	28	27
6-8	29	29	29	27
9-11	31	31	31	29
12-15	33	33	33	31
16-17	37	37	36	35
18-19	36	35	35	33

Data taken from Tables 2 and 3, pp 25, and 26; MRID 44802105.
*Significantly different from control; $p \leq 0.05$.

5. Cesarean section data

Cesarean section data are summarized in Table 3. There were no statistically significant or treatment-related differences in pregnancy rate, mean number of corpora lutea and implantation sites, pre- and postimplantation losses, resorptions, viable fetuses, fetal weights, sex ratios, and placental weights at any treatment level. No fetal deaths were observed.

TABLE 3. Cesarean section observations in rats				
Observations	Dose in mg/kg/day			
	0	40	200	1000
No. Animals Assigned	25	25	25	25
No. Animals Pregnant	24	24	24	23
Pregnancy Rate (%)[a]	96	96	96	92
Maternal Mortality	1	0	0	0
Delivered Early/Aborted	0	0	0	0
Total Corpora Lutea[a]	403	427	401	370
Corpora Lutea/Dam	16.8±2.2	17.8±2.5	16.7±2.7	16.1±1.9
Total Implantations[a]	370	386	377	352
Implantations/Dam	15.4±1.7	16.1±.2.8	15.7±3.3	15.3±1.6
Preimplantation Loss (%)	8.4	10.4	7.6	6.4
Postimplantation Loss (%)	4.6	5.4	5.3	7.7
Total Resorptions[a]	17	22	19	28
Early Resorptions/Dam	0.7±0.8	0.9±0.9	0.8±0.9	1.2±1.1
Late Resorptions/Dam	0.0	0.0	0.0	0.0
Dams with Viable Fetuses	24	24	24	23
Total Live Fetuses[a]	353	367	358	324
Live Fetuses/Litter	14.7±2.1	15.3±2.6	14.9±3.2	14.1±1.8
Live Males/Litter	7.6±2.0	8.4±2.5	7.6±2.2	7.5±2.2
Live Females/Litter	7.0±2.5	6.8±2.2	7.3±2.5	6.6±2.1
Dead Fetuses	0	0	0	0
Live Mean Fetal Weight (g)	3.74±0.05	3.74±0.06	3.73±0.07	3.77±0.07
Live Weight/Male Fetus (g)	3.83±0.21	3.84±0.23	3.84±0.22	3.87±0.19
Live Weight/Female Fetus (g)	3.64±0.22	3.61±0.22	3.61±0.18	3.67±0.22
Sex Ratio (% Male)[a]	51.7	54.9	51.0	53.2
Mean placental weight (g)	0.56±0.02	0.53±0.02	0.56±0.02	0.56±0.02

Data taken from Table 4, page 28; MRID 44802105.
[a]Calculated by reviewer..

B. DEVELOPMENTAL TOXICITY

Fetal external, visceral, and skeletal variations, and skeletal ossification are summarized in Table 4.

1. External examination

As shown in Table 4., there were no statistically significant ($p \leq 0.05$) or treatment-related external malformations or variations observed in fetuses at any dose level. Increased incidence of large fetuses at 1000 mg/kg/day (10.5%) were within the range of historical controls and large placentas at 1000 mg/kg/day (6.2%) were just outside the upper range for historical controls and not considered to be biologically relevant.

2. Visceral examination

Although a variety of visceral variations were observed (Table 4), the incidences were within the range of historical controls. No statistically significant visceral malformations or variations were observed in any treatment group, compared to controls.

TABLE 4: Summary of findings for examination of fetal external, visceral, and skeletal variations and skeletal ossification [% fetal incidence (# litters)]

Observations	Dose in mg/kg/day				
	0	40	200	1000	Hist. cont. range[a]
External variations					6296 fetuses
#Fetuses (#litters) examined	352 (24)	366 (24)	357 (24)	324 (23)	22 studies
Large fetus (>4.10 g)	9.1 (12)	8.7 (12)	8.1 (12)	10.5 (16)	0.7-16.3
Large placenta (>0.70 g)	4.5 (6)	3.6 (8)	5.6 (9)	6.2 (9)	0.0-5.0
Visceral variations					2466 fetuses
#Fetuses (#litters) examined	173 (24)	177 (24)	171 (24)	158 (23)	16 studies
Unilateral hydroureter	0.6 (1)	0.5 (1)	1.1 (2)	1.2 (2)	0.0-2.2
Hepatic hemorrhages	22.0 (17)	21.5 (16)	33.3 (21)	23.4 (19)	5.3-21.7
Small additional liver lobe	13.3 (13)	12.4 (18)	15.2 (16)	13.9 (16)	6.4-17.2
Testes slightly displaced	22.6 (12)	23.7 (14)	22.4 (16)	21.3 (12)	11.0-47.0
Cervical subcutaneous hemorrhage	5.8 (8)	13.0 (13)	14.0 (15)	7.6 (9)	0.0-17.2
Scapular subcutaneous hemorrhage	28.9 (19)	29.9 (19)	32.2 (19)	22.8 (13)	10.1-40.4
Fore/hind-limb subcutaneous hemorrhage	21.4 (15)	24.3 (14)	25.1 (16)	12.7 (11)	6.3-32.2
Abdominal subcutaneous hemorrhage	20.8 (14)	26.0 (17)	24.6 (14)	12.7 (9)	0.0-20.2
Skeletal variations					2683 fetuses
#Fetuses (#litters) examined	179 (24)	189 (24)	186 (24)	166 (23)	16 studies
Bilateral ribs 13/13 (normal)	83.2 (24)	77.8 (24)	76.9 (24)	68.7 (22)	75.4-99.0
Unilateral supernumerary ribs 13/14	11.7 (11)	13.2 (18)	13.4 (13)	16.9 (15)	0.0-15.9
Bilateral supernumerary ribs 14/14	5.0 (3)	9.0 (6)	9.7 (9)	14.5 (9)	0.0-10.4
Skeletal ossification					2683 fetuses
#Fetuses (#litters) examined	179 (24)	189 (24)	186 (24)	166 (23)	16 studies
Medium anterior fontanelle	96.1 (24)	97.9 (24)	96.8 (24)	95.2 (23)	91.6 -100.0
Inc. ossification of interparietal bone	13.4 (13)	18.5 (13)	7.5 (8)	13.3 (17)	15.4-38.3
Inc. ossification of hyoid bone	3.9 (3)	7.9 (9)	5.9 (10)	9.6 (11)	0.0-14.8
Inc. ossification of 1 sternebra	36.3 (20)	28.0 (18)	24.7 (17)	39.8 (18)	13.1-40.6
Inc. ossification ot 2 sternebra	40.2 (24)	45.0 (23)	45.7 (22)	42.2 (20)	31.1-51.4
Inc. ossification of 3 sternebra	19.6 (16)	20.1 (16)	22.6 (19)	15.1 (14)	18.1-37.2
Oss. of ventral arch of 1st cervical vert.	10.6 (12)	6.9 (7)	10.8 (11)	15.1 (13)	4.0-25.7
Inc. oss. of 1 or more throacic vert. centra	18.4 (13)	14.8 (16)	19.9 (15)	14.5 (13)	12.9-23.4
Inc. oss. of 1st lumbar vertebral centrum	0.0 (0)	0.0 (0)	0.0 (0)	0.6 (1)	0.0-0.7
25 pre-sacral vertebrae	0.0 (0)	0.0 (0)	0.0 (0)	0.6 (1)	0.0-4.5
27 pre-sacral vertebrae	0.6 (1)	0.0 (0)	0.0 (0)	1.2 (1)	0.0-2.2
Metacarpals/metatarsals 3/4	77.7 (23)	73.5 (24)	60.8 (23)	69.9 (23)	63.8-83.6
Metacarpals/metatarsals 4/4	20.7 (14)	25.4 (15)	37.6 (20)	29.5 (19)	13.1-34.4

Data taken from Tables 6-8, pp. 29-38; MRID 44802105.
[a]% Fetuses affected.

3. Skeletal examination

No statistically significant or treatment-related increases in fetal skeletal malformations were observed in any treatment group. Although a variety of skeletal variations were observed, most were random and sporadic and occurred within the incidences for historical controls. The incidences of unilateral and bilateral supernumerary ribs were increased for the 1000 mg/kg/day treatment group. Although not statistically significantly increased over controls, the incidences of unilateral and bilateral supernumerary ribs are sufficiently outside the range for historical controls that the study authors consider these observations treatment-related. The decreased incidence of normal ribs at 1000 mg/kg/day supports this conclusion. A variety of incidences of reduced or incomplete ossification were observed at all treatment levels which were within the range of historical controls and were not considered an indication of reduced fetal growth at any treatment level (Table 4).

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 1000 mg/kg/day a marginal decrease in absolute body weight was observed during GD 3-20 and there was a statistically significant ($p \leq 0.05$; 14.5%) decrease in net body weight change from GD 12-16. A marginal reduction in food consumption was observed throughout the treatment and post-treatment periods at 1000 mg/kg/day. On the basis of a statistically significantly decreased body weight gain (14.5%) during GD 12-16 and marginally reduced food intake during the treatment period at 1000 mg/kg/day, the LOAEL for maternal toxicity was 1000 mg/kg/day and the NOAEL was 200 mg/kg/day.

There were no statistically significant or treatment-related changes in gestational or cesarean section parameters at any treatment level. No biologically significant or treatment-related differences in external malformations/variations, visceral malformations/variations, or skeletal malformations/ossification reduction were observed in fetuses at any treatment level including controls. At 1000 mg/kg/day, there was an increased incidence of bilateral supernumerary ribs that, although not statistically significant, was considered to be treatment-related. On the basis of the increased incidence of supernumerary ribs, the LOAEL was 1000 mg/kg/day and the NOAEL was 200 mg/kg/day for RPA400727.

B. REVIEWER'S DISCUSSION

1. MATERNAL TOXICITY

No mortality, abortions, or treatment-related clinical signs of toxicity were observed in any treatment group. Food consumption was marginally reduced (5.4-8.3%)

throughout the treatment and post-treatment periods at 1000 mg/kg/day, but was not statistically significantly different from controls. At the 1000 mg/kg/day dose level, there was also a marginal reduction in mean body weight (1.9-4.1%) during the treatment and post-treatment periods (GD 6-19) and a statistically significant reduction in mean body weight gain ($p \leq 0.05$; 14.5%) during GD 12-16. There were no statistically or biologically significant gross necropsy observations at maternal sacrifice. No treatment-related maternal changes were noted at 40 or 200 mg/kg/day.

Therefore, the maternal toxicity LOAEL is 1000 mg/kg/day based on significantly decreased body weight gain during GD 12-16 and the maternal toxicity NOAEL is 200 mg/kg/day.

2. DEVELOPMENTAL TOXICITY

a. Deaths/resorptions

Treatment with RPA400727 did not cause an increase in the number of dead fetuses or changes in total corpora lutea, implantation sites or resorptions/dam. No fetal deaths were recorded during the study.

b. Altered growth

No statistically significant or treatment-related differences in fetal weights or mean placental weights of viable fetuses were observed at any treatment level compared to controls. No significantly delayed maturation of fetuses (retardation of skeletal ossification) was observed at any treatment level.

c. Developmental variations

No statistically significant or treatment-related differences in external or visceral variations were observed in any treatment group compared to controls. Although a range of these variations were observed, there were no biologically or statistically significant differences between treatment and control fetuses. All external and visceral variation occurrences were either random and sporadic, not dose-related, or occurred within the range for historical controls. At 1000 mg/kg/day, increased incidences of supernumerary ribs were observed. Although not significantly different from controls, the incidences at 1000 mg/kg/day were greater than the upper limits for historical controls and these skeletal variations were considered treatment-related.

d. Malformations

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

Therefore, the developmental toxicity LOAEL is 1000 mg/kg/day based on increased incidences of unilateral and bilateral supernumerary ribs and the developmental toxicity NOAEL is 200 mg/kg/day.

C. STUDY DEFICIENCIES

No deficiencies were observed which would adversely affect the interpretation 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 (§83-3a)]**.