Mackenzie (1982)

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REPORT

Teratology Study with Rotenone in Rats

Study No. 81178

for

U.S. Fish and Wildlife Service
La Crosse, Wisconsin

Contract No. FWS-14-16-0009-81-043

by

Hazleton Raltech, Inc.
A Subsidiary of Hazleton Laboratories America, Inc.
3301 Kinsman Boulevard
Madison, Wisconsin 53704

June 17, 1982

STUDY SUMMARY

PROTOCOL TP-179

Teratology Study with Rotenone in Rats

STUDY NUMBER

81178

TEST MATERIAL

Rotenone

PROJECT DIRECTOR

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STUDY TIMETABLE

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QUALITY ASSURANCE FINAL REPORT STATEMENT

Teratology Study With Rotenone in Rats

Study #81178

The final report as herein attached for the above-mentioned study has been reviewed by the assigned Quality Assurance Unit of Hazleton Raltech, Inc. in accordance with the Good Laboratory Practice Regulations as set forth in 21 CFR 58.35 (b) (6) (7). It has been found to accurately identify and/or describe the authorized methods and standard operating procedures followed in the conduct of the study and that the reported data accurately reflect the raw data of the laboratory study. Furthermore, the Quality Assurance Unit has conducted the following inspections of the testing facilities utilized in the conduct of this study and has submitted written reports of said inspections to the study director and/or management.

Date of Inspection	Type of Inspection	Date Issued to Management
9/21/81	Protocol Review	9/21/81
11/13/81	Test Article Preparation	11/13/81
11/18/81	Test Article Administration Body Weight Data Collection Animal/Cage Identification	11/18/81
11/30/81	Necropsy Tissue Collection	11/30/81
5/03/82	Final Report Review	5/03/82

Susan Glad Anderson

Susan Glad Anderson, Manager
Quality Assurance Unit

DATE June 17, 1982

OBJECTIVE

This study was designed to evaluate the potential embryofetal toxicity and/or teratogenicity of rotenone administered by oral gavage to pregnant rats on Days 6 through 19 of gestation. An earlier teratology study with rotenone (Teratology Study for Safety Evaluation of Rotenone Using Rats, Contract #14-16-0009-78-088, Environmental Consultants, Inc., Norfolk, Virginia) did not establish a no-effect level. Therefore, a decision was made by the Fish and Wildlife Service in consultation with the Environmental Protection Agency (EPA) to conduct another teratology study. All aspects of this study were in compliance with the proposed EPA Good Laboratory Practice Regulations.[1]

PERSONNEL

Study Director	Karen M. MacKenzie, PhD
Study Supervisor	Susan M. Dickie, BA
Biostatistician	Brian R. Mitchell, MS

TEST MATERIAL

The test material used in this study was rotenone, and was supplied by the U.S. Fish and Wildlife Service, National Fishery Research Laboratory, La Crosse, Wisconsin. The stability of rotenone in corn oil stored under ambient conditions (in amber glass bottles at room temperature) was confirmed in a previous study (Raltech Study No. 80050, Teratology Study with Rotenone in Mice).

To ensure that the prescribed dosage levels of rotenone were administered during this study, duplicate samples were taken from one set of test solutions on the day it was prepared (11/13/81) and on the last day it was administered to the test animals (11/19/81) and subsequently analyzed for rotenone concentration by Hazleton Raltech, Inc. (Appendix J)

TEST SYSTEM

Test Animal

Young adult COBS® CD® rats (7 to 10-week-old virgin females and males) were purchased from Charles River Breeding Laboratories (Kingston facility) Wilmington, Massachusetts. The albino rat was used as the test animal in this study per registration guidelines.[2] The rats were acclimated in the test facility for a minimum of 2 weeks prior to mating.

Mated rats were obtained by housing each virgin female with one male. The females were checked daily for the presence of a vaginal plug or sperm in the vaginal smear. The day a plug or sperm was found was considered Day 0 of gestation and the mated rat was caged individually. Since all mated females were not obtained on one day, each group of mated animals was distributed at random daily among test and control groups using a computer-generated random number table.

equivalent, Sigma Chemical Company, St. Louis, Missouri; 5 ml/kg/day) according to the same treatment regimen. Each treatment group consisted of a minimum of 25 mated female rats.

Group	Treatment	Total Daily Dose Rotenone (mg/5 ml corn oil/kg)	Number of Mated Female Rats
1	Vehicle Control	0	25
2	Rotenone	0.75	25
3	Rotenone	1.5	25
4	Rotenone	3	25
5	Rotenone	6	25

The doses used in this study were selected based on the results of an earlier study (Environmental Consultants, Inc., Teratology Study for Safety Evaluation of Rotenone Using Rats, Contract #14-16-0009-78-088) which indicated that 6 mg T930/kg was toxic in rats.

Observations

The body weight of each mated female was recorded on gestation Days 0, 6 (first day of treatment, used to determine individual animal's daily dosage), 9, 12, 15, 18, and at the time of sacrifice on Day 20 (actual and corrected by subtracting gravid uterine weight). Initial body weights for animal No. 63119331 to 63119336 were inadvertently recorded on Day 1 rather than Day 0 of gestation.

Each animal was observed at least once daily throughout the test period for any abnormalities in activity or appearance, or any indication of toxicity, including changes in feed consumption (monitored by visual examination), morbidity, and mortality.

In order to minimize loss of tissues due to autolysis, moribund animals were sacrificed if they were not expected to survive until the next observation period. Data from these animals are reported separately.

On Day 20 of gestation, the dams in each treatment group were sacrificed by the procedures described below.

Necropsy

The dams were weighed and then euthanatized with CO_2. A midline laparotomy was performed and the entire reproductive tract was removed, including both ovaries. The ovaries were removed from the uterine tract, examined for gross abnormalities, and the number of corpora lutea (CL) was recorded. The gravid uterus was weighed. After external examination, it was opened along its entire length, conceptuses were removed, placental membranes incised, and the following information was recorded: the number and location of live and dead fetuses, early and late resorptions, empty sites and implantation scars; unusual coloration and variations in amniotic fluid or placentae; and any other abnormalities. Uteri which appeared to be nongravid were opened and placed in a 10% solution of ammonium sulfide to confirm pregnancy status.

- Number and percent of live fetuses
- Number and percent of dead fetuses
- Number and percent of resorbed fetuses
- Mean live fetal weight
- Sex ratio [(M/M+F) x 100]

The following abnormality data are included for each litter:

- Identification number of dam
- Number and percent of fetuses with gross external abnormalities
- Number of fetuses examined for soft tissue abnormalities
- Number and percent of fetuses having soft tissue abnormalities
- Number of fetuses examined for skeletal abnormalities
- Number and percent of fetuses having skeletal abnormalities
- Incidence and full description of each type of abnormality
- A photograph of an abnormality was provided when it was difficult to describe

The following data are included for each dose level:

- Identification of the dose level
- Number of litters examined
- Mean number of CL per litter
- Mean number of implantations per litter
- Mean implantation efficiency
- Total live fetuses
- Mean number and percent of live fetuses per litter
- Mean live fetal weight
- Mean sex ratio [(M/M + F) x 100]
- Total dead fetuses
- Mean number and percent of dead fetuses per litter
- Total resorbed fetuses
- Mean number and percent of resorbed fetuses per litter
- Number and percent of fetuses bearing abnormalities of each kind observed
- Number and percent of litters having abnormal fetuses

Data Analysis

The litter or dam was considered the experimental unit for evaluation, although data on individual fetuses with abnormalities also were considered.

Dam body weight on Day 0 and the corrected and uncorrected change in weight between Days 0 and 20 were analyzed by analysis of variance, and, when significant, treatment means were compared to control means using Dunnett's multiple comparison test.[6] Dam body weights on Days 6 and 20, gravid uterine weight, and corrected weight on Day 20 were analyzed by covariate analysis using Day 0 body weight as the covariate.[6] Dunnett's test was performed on means adjusted for the covariate where covariate analyses indicated significant differences.[6]

Mean body weight changes between Days 0 and 20 of gestation (uncorrected and corrected) and corrected body weights on Day 20, adjusted for Day 0, were significantly lower than the controls for the 1.5, 3, and 6 mg/kg groups (Table 4).

Observations of Animals Which Died on Test

One animal in the 1.5 mg/kg group (animal No. 4274) and two animals in the 6 mg/kg groups (animals No. 8007 and 8025) died on test on gestation Days 11, 17, and 10, respectively. The rat from the 1.5 mg/kg group exhibited tonic convulsions following treatment. No abnormal observations were noted at necropsy. The two animals from the 6 mg/kg group displayed excessive salivation and rubbing of the face and paws on the bottom of the cage following treatment and had a reddish-brown tinge on the fur during the treatment interval. In addition, animal No. 8007 had a rough coat, nasal exudate, excessive salivation prior to and following treatment, a wet urogenital area, and was lethargic following treatment. At necropsy, the stomach of animal No. 8007 was described as having a negligible amount of food and being filled with oil. No abnormal observations were noted for animal No. 8025 at necropsy.

Observations of Animals Which Were Sacrificed on Test

One animal from the 6 mg/kg group (animal No. 8015) was sacrificed on Day 18 of gestation due to its moribund condition. This animal rubbed its face and paws on the bottom of the cage and exhibited salivation prior to and following treatment. In addition, the animal had a wet urogenital area, a rough coat with a reddish-brown tinge on the fur, reddish-brown exudate around the eyes, and had a weight loss of 44 g between Days 15 and 18 of gestation. A yellowish, 4 x 1 mm lesion was found on the left quadrate lobe of the liver at the time of necropsy, and was preserved in 10% neutral buffered formalin for possible future histopathological evaluation.

Cesarean Sections

Data concerning the prenatal effects of rotenone are summarized in Table 5 and individual litter data are presented in Appendix C.

The pregnancy rate for all groups ranged from 96% to 100%. All females with fetuses at the time of scheduled cesarean section had viable litters. A single dead fetus was reported in one litter in the 1.5 mg/kg group (animal No. 4267).

There were no statistically significant differences in the mean number of corpora lutea or implants, implantation efficiency, litter size, sex ratio, or in the mean number or percent of live, resorbed, or dead fetuses. Mean live fetal weights were significantly lower ($p \leq 0.05$) for animals treated with 6 mg/kg rotenone.

Common skeletal variations and minor anomalies were present in all groups in a nontreatment-related pattern. Observations most frequently reported included reduced skull bones, unossified hyoids and sternebrae, rudimentary and full unilateral ribs, and centra variations. Other variations observed with less frequency included unossified pubes, misaligned and bipartite sternebrae, wavy and fused ribs, seventh cervical ribs, and 25 and 27 presacral vertebrae. The only major skeletal malformation reported in this study was a single incident of scoliosis with associated rib anomalies in one fetus in the control group (animal No. 4222).

CONCLUSIONS

None of the deaths which occurred during this study (one in the mid dose and two in the highest dose group) was attributable to the test material, rotenone. One animal in the high dose group was sacrificed on test due to moribund conditions. The only observation noted at necropsy was the presence of a lesion on the liver which was considered inconclusive.

Clinical signs reported most frequently observed in all treatment groups throughout the study included excessive salivation and rubbing of the face and paws on the bottom of the cage following treatment. In addition, frequent observations of rough coat, reddish-brown tinge on the fur, nasal exudate, lethargy, poor muscle tone, and a wet urogenital area were noted. No abnormal observations were noted in the control group.

Mean body weight changes between Day 0 and 20 of gestation (uncorrected and corrected) and corrected body weights on Day 20, adjusted for Day 0, were significantly lower than the controls for the 1.5, 3, and 6 mg/kg groups.

There were no statistically significant differences in the mean number of corpora lutea or implants, implantation efficiency, litter size, sex ratio, or in the mean number or percent of live, resorbed, or dead fetuses. Mean live fetal weights for the highest dose group were significantly lower when compared to the controls ($p \leq 0.05$).

The only gross abnormality observed in this study was the presence of clear, raised, dermal cysts on one fetus in one litter from the low dose group and two fetuses in one litter from the mid dose group.

Minor fetal soft tissue anomalies were present in all groups in a nontreatment-related pattern. Major malformations consisting of dilated lateral ventricles of the brain and microphthalmia were observed in one fetus from the vehicle control group. A single incident of cleft palate in one fetus from the low dose group was the only major malformation noted in any of the treatment groups and is not considered to be treatment-related.

Common skeletal variations and minor anomalies were present in all groups in a nontreatment-related pattern. The only major skeletal malformation reported in this study was a single incident of scoliosis with associated rib anomalies in one fetus from the vehicle control group.

Based on the results of this study, rotenone does not appear to be fetotoxic or teratogenic when administered at doses of 6 mg/kg or less.

Study No. 81178

Table 1

Survival of Mated Rats Treated with Rotenone[a]

Rotenone (mg/kg)	Number of Rats Treated	Rats Dead on Gestation Days						Rats Alive on Day 20	
		0-5	6-8	9-11	12-14	15-17	18-20	Number	Percent
0	25	0	0	0	0	0	0	25	100
0.75	25	0	0	0	0	0	0	25	100
1.5	25	0	0	1[b]	0	0	0	24	96
3	25	0	0	0	0	0	0	25	100
6	25	0	0	1[b]	0	1[b]	1[c]	22	88

[a]Rotenone was administered daily by oral gavage on Days 6-19 of gestation.
[b]Died on test.
[c]Sacrificed on test.

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Table 2 (Continued)

Daily Observations of Mated Rats[a]

Animal Number	Day of Gestation	Observation
63114243	10	Mild salivation following treatment.
	11,12	Rubbing of face and paws on bottom of cage following treatment.
63114244	9	Mild salivation following treatment.
63114246	16,18,19	Excessive salivation following treatment.
63114247	13	Excessive salivation following treatment.
	15-19	Rubbing of face and paws on bottom of cage following treatment.
63114248	13,14,18,19	Rubbing of face and paws on bottom of cage following treatment.
	18,19	Excessive salivation following treatment.
63119331	9,11,12	Rubbing of face and paws on bottom of cage following treatment.
	16,17,18	Excessive salivation following treatment.
63119332	8-19	Rubbing of face and paws on bottom of cage following treatment.
63119333	17-19	Excessive salivation following treatment.
63119334	16-19	Excessive salivation following treatment.

[a]Animals for whom no observations were recorded are not included in this table.

Study No. 81178

Table 2 (Continued)

Daily Observations of Mated Rats[a]

Animal Number	Day of Gestation	Observation
63114265	9-12,19	Excessive salivation following treatment.
	13,14,17	Rubbing of face and paws on bottom of cage following treatment.
63114266	11,12,17	Rubbing of face and paws on bottom of cage following treatment.
63114267	11,12	Rubbing of face and paws on bottom of cage following treatment.
63114268	8-11,13,18	Excessive salivation following treatment.
63114269	13-17	Rubbing of face and paws on bottom of cage following treatment.
		Excessive salivation following treatment.
63114271	13,14,16-19	Rubbing of face and paws on bottom of cage following treatment.
	17-19	Excessive salivation following treatment.
63114272	17	Excessive salivation following treatment.
63114273	15-19	Excessive salivation following treatment.
63114274	11	Tonic convulsions following treatment.
		Died on test.

[a]Animals for whom no observations were recorded are not included in this table.

Study No. 81178

Table 2 (Continued)

Daily Observations of Mated Rats[a]

Animal Number	Day of Gestation	Observation
63114280	11-14,18,19	Excessive salivation following treatment.
63114281	15-17,19	Rubbing of face and paws on bottom of cage following treatment.
63114282	11-14	Excessive salivation following treatment.
	12-14,16-20	Reddish-brown nasal exudate.
	15-17,19	Rubbing of face and paws on bottom of cage following treatment.
	15-20	Rough coat.
63114284	10-13,15,18	Excessive salivation following treatment.
	14-16,18,19	Rubbing of face and paws on bottom of cage following treatment.
63114285	14-16,18,19	Rubbing of face and paws on bottom of cage following treatment.
63114286	9-17	Rough coat.
	12,13	Excessive salivation following treatment.
	14-16,18,19	Rubbing of face and paws on bottom of cage following treatment.
63114287	14-16,18	Excessive salivation following treatment.
	18,19	Rubbing of face and paws on bottom of cage following treatment.

[a]Animals for whom no observations were recorded are not included in this table.

Study No. 81178

Table 2 (Continued)

Daily Observations of Mated Rats[a]

Animal Number	Day of Gestation	Observation
63114296	7-19	Excessive salivation following treatment.
	14-19	Rubbing of face and paws on bottom of cage following treatment.
		Rough coat.
		Reddish-brown tinge on fur.
63114297	12,14-18	Excessive salivation following treatment.
63114298	6,7,9,14-16	Excessive salivation following treatment.
	8-10,12-14,17-19	Rubbing of face and paws on bottom of cage following treatment.
	8-14	Rough coat.
63114299	16-19	Excessive salivation following treatment.
63114300	15-19	Excessive salivation following treatment.
	6 mg Rotenone/kg	
63118001	10-18	Rubbing of face and paws on bottom of cage following treatment. Reddish nasal exudate. Reddish-brown tinge on fur. Rough coat. Excessive salivation following treatment.
	12,15,17	Excessive salivation prior to treatment.
	14-19	Lethargic following treatment.

[a]Animals for whom no observations were recorded are not included in this table.

Study No. 81178

Table 2 (Continued)

Daily Observations of Mated Rats[a]

Animal Number	Day of Gestation	Observation
63118005	9-19	Rubbing of face and paws on bottom of cage following treatment. Rough coat. Wet urogenital area. Excessive salivation following treatment.
	9-20	Reddish nasal exudate. Reddish-brown tinge on fur.
	11-14,17	Excessive salivation prior to treatment.
	13-20	Lethargic following treatment.
	20	Reddish eye exudate.
63118006	9-12	Rubbing of face and paws on bottom of cage following treatment. Rough coat. Wet urogenital area.
	9-12,20	Reddish nasal exudate. Reddish-brown tinge on fur.
	11	Excessive salivation prior to treatment.
	9-12,15,16,18,19	Excessive salivation following treatment.
	17-20	Alopecia on ventral surface.
	20	Reddish eye exudate.
63118007	9-16	Rubbing of face and paws on bottom of cage following treatment. Reddish nasal exudate. Rough coat. Excessive salivation following treatment.
	11	Excessive salivation prior to treatment.
	13-16	Lethargic following treatment.
	16	Wet urogenital area.
	17	Died on test.
63118008	9-19	Rubbing of face and paws on bottom of cage following treatment. Reddish nasal exudate. Rough coat. Excessive salivation following treatment.

[a]Animals for whom no observations were recorded are not included in this table.

Study No. 81178

Table 2 (Continued)

Daily Observations of Mated Rats[a]

Animal Number	Day of Gestation	Observation
63118013	8-12,14-19	Excessive salivation following treatment.
	10,19	Excessive salivation prior to treatment.
	9-20	Rough coat.
63118014	8-12,15,17-19	Excessive salivation following treatment.
	9-15,18,19	Rough coat.
	11-20	Thick, white, opaque film across top half of right eye.
	14-16,18,19	Rubbing of face and paws on bottom of cage following treatment.
	10,17	Excessive salivation prior to treatment.
63118015	7-12,15,16	Excessive salivation following treatment.
	8-14	Rough coat.
	9,12,15,16	Excessive salivation prior to treatment.
	11-14,16-18	Rubbing of face and paws on bottom of cage following treatment.
	17,18	Reddish-brown exudate around eyes. Rough coat.
		Reddish-brown tinge on fur. Wet urogenital area.
	18	Sacrificed on test.
63118017	7-19	Excessive salivation following treatment.
	9,15,16,19	Excessive salivation prior to treatment.
	11,12,17-19	Rubbing of face and paws on bottom of cage following treatment.
	13-17,19,20	Reddish-brown exudate around mouth and nasal region.
		Reddish-brown tinge on fur.

[a]Animals for whom no observations were recorded are not included in this table.

Study No. 81178

Table 2 (Continued)

Daily Observations of Mated Rats[a]

Animal Number	Day of Gestation	Observation
63118023	8-19	Excessive salivation following treatment.
	9-20	Reddish-brown nasal exudate. Reddish-brown tinge on fur.
	14-19	Rubbing of face and paws on bottom of cage following treatment.
63118024	8-19	Excessive salivation following treatment.
	9,10,12-20	Rough coat.
	11-20	Reddish-brown tinge on fur.
	15,16	Rubbing of face and paws on bottom of cage following treatment.
63118025	8,9	Rubbing of face and paws on bottom of cage following treatment.
	9	Reddish-brown tinge on fur.
	10	Died on test.
63119336	10-19	Rubbing of face and paws on bottom of cage following treatment.
	10-19	Excessive salivation following treatment.
	11-20	Rough coat.

[a]Animals for whom no observations were recorded are not included in this table.

Table 4

Summary of Mean Body Weights and Gravid Uterine Weights[a]

Rotenone (mg/kg)	Body Weight on Gestation Day							Weight Change 0 to 20	Gravid Uterine Weight (GU)	Corrected Day 20 Weight (20-GU)	Corrected Weight Change (20-GU-0)
	0[b]	6	9	12	15	18	20				
0	249	275	282	298	313	351	379	130	69.9	309	60
S[c]	17.9	20.8	19.1	21.0	21.6	24.8	27.6	16.9	12.3	22.4	10.1
N[c]	24	24	24	24	24	24	24	24	24	24	24
0.75	249	276	284	301	315	352	381	132	72.7	307	59
S	19.8	20.8	22.7	22.6	23.2	22.7	26.3	18.2	15.0	25.9	14.0
N	25	25	25	25	25	25	25	25	24[d]	24	24
1.5	241	267	275	287	303	338	365	124*	70.1	295**	54**
S	16.6	20.9	20.8	20.4	19.3	23.0	26.9	17.0	15.4	22.4	12.0
N	23	23	23	23	23	23	23	23	23	23	23
3	234*	261	266	281	295	328	356	122**	72.2	284**	50**
S	20.9	22.1	23.0	24.5	24.8	28.2	31.0	17.4	11.5	24.2	12.6
N	24	24	24	24	24	24	24	24	24	24	24
6	240	266	266	276	284	301	316	76**	57.6	258**	24**
S	20.0	22.9	18.1	19.6	21.2	22.3	26.2	26.5	9.0	21.5	13.8
N	22	22	22	22	22	22	22	22	22	22	22

[a]Mean weights (expressed in grams) were calculated using data from animals which were pregnant at the time of necropsy.
[b]Includes values for six animals weighed on Day 1 rather than Day 0.
[c]S: Standard deviation.
N: Number of data points.
[d]Gravid uterus from one animal inadvertently not weighed.
*Significantly different from control ($p \leq 0.05$).
**Significantly different from control ($p \leq 0.01$).

Study No. 81178

Table 5 (Continued)

Summary of Mean Data from Cesarean Sections
Performed on Day 20 of Gestation[a]

Rotenone (mg/kg)	Treatment Group 0	0.75	1.5	3	6
Litters with dead fetuses	0	0	1	0	0
Total dead fetuses	0	0	1	0	0
Dead Fetuses					
Mean	0	0	0	0	0
S[b]	0.0	0.0	0.2	0.0	0.0
Percent dead fetuses					
Mean	0.0	0.0	0.3	0.0	0.0
S	0.00	0.00	1.39	0.00	0.00
Litters with resorbed fetuses	14	16	16	13	9
Total resorbed fetuses	31	37	29	17	12
Resorbed fetuses					
Mean	1	1	1	1	1
S	1.5	1.9	1.4	0.8	0.7
Percent resorbed fetuses					
Mean	8.7	10.2	9.7	4.8	3.6
S	9.35	13.68	11.54	5.18	4.82

[a]Only data from animals which were pregnant at the time of scheduled cesarean section are included in mean values reported in this table.
[b]S: Standard deviation.

TABLE 7 --ABNORMALITIES IN GROSS EXAM
TERATOLOGY STUDY WITH ROTENONE IN RATS

GROUP	A	B	C	D	E
NUMBER OF LITTERS EXAMINED	24	25	23	24	22
NUMBER OF FETUSES EXAMINED	314	331	304	329	310
NUMBER (PERCENT) OF LITTERS AFFECTED					
CRANIUM					
CYST(S)	0	1 (4.0)	1 (4.3)	0	0

TABLE 9 --ABNORMALITIES IN SOFT TISSUE
TERATOLOGY STUDY WITH ROTENONE IN RATS

GROUP	A	B	C	D	E
NUMBER OF LITTERS EXAMINED	24	25	23	24	23
NUMBER OF FETUSES EXAMINED	152	165	145	162	161
NUMBER (PERCENT) OF FETUSES AFFECTED					
BRAIN					
DILATATION	1 (0.7)	0	0	0	0
LATERAL VENTRICLES					
EYE					
MICROPHTHALMIA-UNILATERAL	1 (0.7)	0	0	0	0
PALATE					
CLEFT	0	1 (0.6)	0	0	0
AORTIC ARCHES					
ACCESSORY SUBCLAVIAN ARTERY	0	0	1 (0.7)	2 (1.2)	0
KIDNEYS					
RENAL PELVIC CAVITATION-BILATERAL	0	0	2 (1.4)	0	1 (0.6)
RENAL PELVIC CAVITATION-UNILATERAL	1 (0.7)	1 (0.6)	2 (1.4)	1 (0.6)	2 (1.2)
URETER					
DISTENDED-BILATERAL	0	0	2 (1.4)	0	0
DISTENDED-UNILATERAL	0	1 (0.6)	1 (0.7)	0	0

TABLE 11 --ABNORMALITIES IN SOFT TISSUE
TERATOLOGY STUDY WITH ROTENONE IN RATS

GROUP	A	B	C	D	E
NUMBER OF LITTERS EXAMINED	24	25	23	24	23
NUMBER OF FETUSES EXAMINED	152	165	145	162	161
MEAN PERCENT OF LITTER AFFECTED					
BRAIN					
DILATATION LATERAL VENTRICLES	0.5	0.0	0.0	0.0	0.0
EYE					
MICROPHTHALMIA-UNILATERAL	0.5	0.0	0.0	0.0	0.0
PALATE					
CLEFT	0.0	1.3	0.0	0.0	0.0
AORTIC ARCHES					
ACCESSORY SUBCLAVIAN ARTERY	0.0	0.0	0.6	1.4	0.0
KIDNEYS					
RENAL PELVIC CAVITATION-BILATERAL	0.0	0.0	1.2	0.0	0.6
RENAL PELVIC CAVITATION-UNILATERAL	0.6	0.7	1.3	0.5	1.3
URETER					
DISTENDED-BILATERAL	0.0	0.0	1.2	0.0	0.0
DISTENDED-UNILATERAL	0.0	0.7	0.6	0.0	0.0

TABLE 12 --ABNORMALITIES IN SKELETAL TISSUE
TERATOLOGY STUDY WITH ROTENONE IN RATS

GROUP	A	B	C	D	E
NUMBER OF LITTERS EXAMINED	24	25	23	24	22
NUMBER OF FETUSES EXAMINED	162	166	159	167	157
NUMBER (PERCENT) OF FETUSES AFFECTED					
THORACIC VERTEBRAE (CONTINUED)					
DUMBBELL CENTRA	1 (0.6)	3 (1.8)	3 (1.9)	5 (3.0)	5 (3.2)

TABLE 13 --ABNORMALITIES IN SKELETAL TISSUE
TERATOLOGY STUDY WITH ROTENONE IN RATS

GROUP	A	B	C	D	E
NUMBER OF LITTERS EXAMINED	24	25	23	24	22
NUMBER OF FETUSES EXAMINED	162	166	159	167	157
NUMBER (PERCENT) OF LITTERS AFFECTED					
THORACIC VERTEBRAE (CONTINUED)					
DUMBBELL CENTRA	1 (4.2)	3 (12.0)	2 (8.7)	4 (16.7)	2 (9.1)

TABLE 14 --ABNORMALITIES IN SKELETAL TISSUE
TERATOLOGY STUDY WITH ROTENONE IN RATS

GROUP	A	B	C	D	E
NUMBER OF LITTERS EXAMINED	24	25	23	24	22
NUMBER OF FETUSES EXAMINED	162	166	159	167	157
MEAN PERCENT OF LITTER AFFECTED					
THORACIC VERTEBRAE (CONTINUED)					
DUMBBELL CENTRA	0.6	2.0	1.4	3.2	3.0

APPENDIX A

Body Weight and Gravid Uterine Weight Data for Individual Animals