DATA EVALUATION RECORD

CHLOROTHALONIL

Study Type: §83-3a; Developmental Toxicity Study in Rats

Work Assignment No. 2-01-35 C; formerly 1-01-35 C (MRID 45710207)

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

Prepared by
Pesticides Health Effects Group
Sciences Division
Dynamac Corporation
1910 Sedwick Road, Building 100, Suite B
Durham, NC 27713

Primary Reviewer:
Michael E. Viana, Ph.D.

Signature: Michael E Viana
Date: 10/11/04

Secondary Reviewer:
John W. Allran, M.S.

Signature: John W. Allran
Date: 10-11-04

Project Manager:
Mary L. Menetrez, Ph.D.

Signature: Mary L Menetrez
Date: 10/12/04

Quality Assurance:
Steven Brecher, Ph.D.

Signature: Steven Brecher
Date: 10/11/04

Disclaimer

This Data Evaluation Record may have been altered by the Health Effects Division subsequent to signing by Dynamac Corporation personnel.

EPA Reviewer: Pramod Terse, DVM, Ph.D.
Registration Action Branch 1, Health Effects Division (7509C)
EPA Work Assignment Manager: P. V. Shah, Ph.D.
Registration Action Branch 1, Health Effects Division (7509C)

Signature:
Date
Signature: PVShah
Date 12/15/05
Template version 11/01

DATA EVALUATION RECORD

TXR#: 0052493

STUDY TYPE: Prenatal Developmental Toxicity Study - Rat; OPPTS 870.3700a [§83-3a]; OECD 414.

PC CODE: 081901

DP BARCODE: D301496
SUBMISSION NO.: None

TEST MATERIAL (PURITY): Chlorothalonil (99.15% a.i.)

SYNONYMS: 2, 4, 5, 6-Tetrachloro - 1, 3 benzodicarbonitrile

CITATIONS: Meyers, D. (1994) Chlorothalonil: a study of the effect on pregnancy of the rat. Huntingdon Research Centre, Ltd., Huntingdon, Cambridgeshire, England. Laboratory Study Identification: HRC Report No.: VCM 22/930637, June 27, 1994. MRID 45710207. Unpublished.

SPONSOR: Vischim S.r.l., Via Friuli, 55 Cesano Maderno, Milan, Italy

EXECUTIVE SUMMARY: In an oral developmental toxicity study (MRID 45710207), Chlorothalonil (Batch # NF 28/01; 99.15% a.i.) in 1.0% methylcellulose was administered daily by gavage at a dose volume of 15 mL/kg bw to 25 female (Crl: CD®[SD] BR VAF/Plus) rats/group at dose levels of 0, 80, 200, or 500 mg/kg/day on gestation days (GD) 6 through 15. All dams were killed on GD 20; their fetuses were removed by cesarean section and examined.

There were no effects of treatment on gross pathology.

At 500 mg/kg/day, one dam was found dead on GD 9. This animal exhibited noisy respiration prior to dosing on the previous day, and post-mortem examination revealed red/brown staining of the perinasal and perioral regions, enlarged cervical lymph nodes, firm lungs with patchy congestion, and gaseous distension of the gastrointestinal tract. Also at the above dose level, two dams were killed for humane reasons on GD 12. These dams exhibited loss of body tone, noisy/irregular respiration, piloerection, and brown perinasal staining immediately prior to death, as well as lethargy, distended abdomen, and yellow stained urogenital region. Post-mortem examination revealed enlarged cervical lymph nodes and severe gaseous distension of the gastrointestinal tract in both animals; one animal was also found to have a roughened forestomach. All other animals survived to study termination. Wet feces were noted on GD 7 or 8 to GD 16, post-dosing salivation was observed in 6/22 dams on GD 11/12, and noisy/irregular respiration was noted in 2/22 dams on GD 10-16 and 13-19. Body weight gains were decreased

($p \leq 0.05$) during treatment on GD 6-8 and 6-14 (decr. 19-41%). Body weight gains continued to be decreased ($p \leq 0.05$) to termination (GD 6-20; decr. 9%) and for the overall (GD 2-20) study (decr. 7%; not significant [NS]). Food consumption was decreased ($p \leq 0.05$) during GD 6-7 (decr. 13%), and water consumption was increased ($p \leq 0.05$) during GD 8-9, 12-13, 14-15, and 18-19 (incr. 21-33%).

The maternal LOAEL is 500 mg/kg bw/day, based on increased mortality, clinical signs of toxicity, decreased body weight gains and food consumption, and increased water consumption. The maternal NOAEL is 200 mg/kg bw/day.

There were no abortions, premature deliveries, or dead fetuses. No effects of treatment were noted on numbers of litters, live fetuses, resorptions (early, late, or complete litter), or on sex ratio or post-implantation losses. No effects of treatment were observed on fetal growth. There were no treatment-related external, visceral, or skeletal malformations or variations.

The developmental LOAEL was not observed. The developmental NOAEL is 500 mg/kg bw/day.

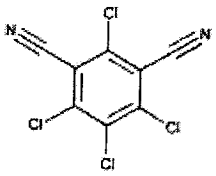
This study is classified **acceptable/guideline (OPPTS 870.3700a)** and satisfies the guideline requirements for a developmental study in the rat. While this study does not satisfy the current guideline requirements for a developmental toxicity study in the rat (daily dosing from implantation to the day before the expected day of parturition), it does satisfy the Pesticide Assessment Guidelines, Subdivision F criteria (November, 1984) in place at the time this study was conducted.

COMPLIANCE: Signed and dated Data Confidentiality, GLP compliance, and Quality Assurance statements were provided. A Flagging statement was provided, but was not signed or dated.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: Chlorothalonil

Description:	White powder
Lot/Batch #:	NF 28/01
Purity:	99.15% a.i.
Compound Stability:	Stable in the vehicle for up to 24 hours (stored at room temperature followed by refrigeration)
CAS #of TGAI:	1897-45-6
Structure:	

2. Vehicle and/or positive control: 1.0% methylcellulose

3. Test animals:

Species:	Rat	
Strain:	Crl: CD®[SD] BR VAF/Plus	
Age/body weight range on GD 0:	8-10 weeks; 166-240 g	
Source:	Charles River UK, Ltd., Margate, Kent, England	
Housing:	Group housed (5/cage) in suspended stainless steel cages with solid sides and wire mesh front, back, top, and floor	
Diet:	Biosure Laboratory Animal Diet No. 1 (manufacturer not provided), *ad libitum*	
Water:	Tap water, *ad libitum*	
Environmental conditions:	**Temperature:**	20±3°C
	Humidity:	53±11%
	Air changes:	Not provided
	Photoperiod:	12 hrs light/12 hrs dark
Acclimation period:	4-5 days	

B. PROCEDURES AND STUDY DESIGN

1. In life dates: Start: January 25, 1993 End: February 9, 1993

2. Mating: Female rats were mated with males of the same strain by the supplier. Confirmation of mating was determined by the detection of spermatozoa in a vaginal smear and/or the presence of a copulation plug. The day on which mating was confirmed was designated as gestation day (GD) 0.

3. Animal assignment: On GD 2, dams were weighed, and animals in the range 174-230 g were randomly allocated (stratified by body weight) to the groups indicated in Table 1. Adjustments were made to the group allocation to ensure an acceptable distribution of females mated to the same male.

Table 1. Animal assignment[a]

Dose (mg/kg bw/day)	0	80	200	500
# Females	25	25	25	25

a Data were obtained from page 14 of the study report.

4. **Dose selection rationale:** It was stated that the dose levels summarized in Table 1 were chosen based on available toxicological data, including the results of a preliminary oral developmental toxicity study (HRC Report No.: VCM 31/930529). In this study, dams were dosed with the test substance at up to 400 mg/kg/day, but a LOAEL was not observed. Therefore, 500 mg/kg/day was chosen as the high dose for the current study, as some maternal toxicity was anticipated at this dose level, and 80 mg/kg/day was expected to be the NOAEL.

5. **Dosage preparation and analysis:** Dosing solutions were prepared fresh each day by adding a weighed amount of test substance to a small amount of 1.0% methylcellulose and grinding with a mortar until a smooth paste was formed. The formulation was gradually made up to final volume and mixed with a high shear homogenizer. Dose formulations were resuspended within 4 hours of preparation and administered within 30 minutes from the commencement of stirring. Samples of the dosing mixtures at each dose level were taken on the first day of treatment, and concentration of the test substance in the vehicle were determined. Homogeneity (top, middle, and bottom) and stability of the test substance in the vehicle were determined in 0.2 and 40 mg/mL preparations. Stability of the test substance in vehicle was measured after 0, 0.5, 1, 4, and 24 hours of storage (described as room temperature during the day followed by refrigeration overnight).

Results

Homogeneity (range as % CV):
0.2 mg/mL: 0.65-1.61%, except 42.2% at 1 hour and 18.3% at 24 hours (see below)
40 mg/mL: 0.08-2.67%

Stability (range as % initial [Time 0]): 91.9-104.8%

Concentration (% nominal)
5.3 mg/mL: 94.5%
13.3 mg/mL: 94.7%
33.3 mg/mL: 99.1%

It was stated that the analytical data indicated that homogeneity of the 0.2 mg/mL formulation was not maintained by stirring for periods greater than 30 minutes and could not be achieved by resuspension following storage for 24 hours. Therefore, it was recommended that dosing be completed within 4 hours of preparation, and that each dose be stirred for a maximum of 30 minutes. With this recommendation, the mixing procedure was adequate and the variation between nominal and actual dosage to the study animals was acceptable.

6. **Dosage administration:** All doses were administered once daily by oral gavage on GDs 6-15 at a volume of 15 mL/kg of body weight. Dosing was adjusted based on the most recent individual body weights.

C. OBSERVATIONS

1. **Maternal observations and evaluations:** All dams were checked for mortality, morbidity, and clinical signs of toxicity daily. Body weights were recorded on arrival and on GD 2, 3, 6, 8, 10, 12, 14, 16, 18, and 20. Food consumption was measured on the same days that body weights were recorded, beginning on GD 3, and reported as group mean values (g/rat/day). Water consumption was measured daily from GD 3 through termination, and reported as group mean values (g/rat/day). On GD 20, all dams were killed by CO_2 asphyxiation, dissected, and examined for congenital abnormalities and macroscopic pathological changes in maternal organs. The gravid uterus was excised, and all fetuses were removed by cesarean section. The numbers of corpora lutea in each ovary and the number and location of all live and dead fetuses and resorptions (early and late) in the uterus were recorded. Uteri or individual uterine horns without visible implantations were examined using a modified Salewski technique. Dams killed *in extremis* or dying prior to scheduled termination were weighed and subjected to a macroscopic examination.

2. **Fetal evaluations:** Live fetuses were weighed and examined for external abnormalities. Approximately half of the fetuses in each litter were fixed in Bouin's solution, and were micro-dissected for visceral examination using Wilson's slicing technique. The remaining fetuses were fixed in 74 OP industrial methylated spirit for subsequent macroscopic examination, evisceration, clearing, and alizarin staining using a modified Dawson technique for skeletal examination. All fetuses were sexed by gonadal inspection after fixation.

D. DATA ANALYSIS

1. **Statistical analyses:** Data were subjected to the following statistical procedures:

Parameter	Statistical test
Maternal body weight gains and food and water consumption	After testing for homogeneity of variance (test not specified), analysis of variance followed by Williams' test if variances homogeneous, or by Kruskal-Wallis analysis followed by Shirley's test if variances heterogeneous
Mean litter data values (numbers of corpora lutea, implants, and live young, pre-implantation and post-implantation losses, early and late resorptions, and litter and mean fetal weights), sex ratio, and skeletal variants	Kruskal-Wallis analysis followed by Shirley's test if necessary. Where 75% or more of the values for a given variable were the same, a Fisher's exact test was used.
Litter distribution of fetal abnormalities	Two-sample permutation test

All tests were two-sided, and significance was denoted at $p \leq 0.05$ and $p \leq 0.01$.

2. **Indices**: The following indices were calculated:

Pre-implantation loss (%) = (# corpora lutea - # implantations)/# corpora lutea x 100

Post-implantation loss (%) = (# implantations - # live young)/# implantations x 100

Additionally, litter weight and mean fetal weight were calculated from the individual fetal weights.

3. **Historical control data**: Historical control data were provided for the mean range and overall mean of fetuses having 14 ribs. Data were comprised of 10 studies performed during or after July, 1991. No other historical control data were provided.

II. RESULTS

A. MATERNAL TOXICITY

1. **Mortality and clinical observations**: At 500 mg/kg/day, one dam was found dead on GD 9. This animal exhibited noisy respiration prior to dosing on the previous day, and post-mortem examination revealed red/brown staining of the perinasal and perioral regions, enlarged cervical lymph nodes, firm lungs with patchy congestion, and gaseous distension of the gastrointestinal tract. Additionally at this dose, two dams were killed for humane reasons on GD 12. These dams exhibited loss of body tone, noisy/irregular respiration, piloerection, and brown perinasal staining immediately prior to sacrifice, as well as lethargy, distended abdomen, and yellow stained urogenital region. Post-mortem examination revealed enlarged cervical lymph nodes and severe gaseous distension of the gastrointestinal tract in both animals; one animal was also found to have a roughened forestomach. All other animals survived to study termination.

At ≥200 mg/kg/day, wet feces were observed from GD 7 or 8 to GD 16 in all cages. Since the rats were group housed, it was assumed all animals were affected. Brown perinasal staining and noisy/irregular respiration were observed sporadically (GD 9-10 and 15-17) in 1/25 dams at 200 mg/kg/day. At 500 mg/kg/day, post-dosing salivation was observed in 6/22 dams on GD 11/12, and noisy/irregular respiration was noted in 2/22 dams on GD 10-16 and 13-19.

2. **Body weight**: Body weights and body weight gains are presented in Table 2. At 500 mg/kg/day, body weight gains were decreased ($p \leq 0.05$) during treatment on GD 6-8 and 6-14 (↓19-41%). Although body weight gains were comparable to controls during the post-treatment interval, cumulative body weight gains continued to be decreased ($p \leq 0.05$) to termination (GD 6-20; ↓9%), with a non-significant decrease of 7% compared to controls for the overall (GD 2-20) study. No other treatment-related effects were observed on body weight or body weight gains.

Table 2. Selected mean maternal body weights and body weight gains (g)[a]

Interval		Dose in mg/kg bw/day (# of Dams)			
		0 (24)	80 (23)	200 (23)	500 (20)
Body weight[b]					
Body weight:	Day 2	202.2	203.1	203.3	204.3
Body weight:	Day 6	237.3	240.0	236.0	240.8
Body weight:	Day 16	314.8	317.7	312.0	305.5
Body weight:	Day 20	374.7	376.8	367.7	365.4
Body weight gain					
Pre-treatment:	Days 2-6[c]	35.1	36.9	32.8	36.5
Treatment:	Days 6-8	14.3	10.8	11.8	8.5** (↓41)
	Days 6-14	57.2	56.0	52.3	46.1* (↓19)
Post-treatment:	Days 16-20[c]	59.9	59.1	55.7	59.9
Overall:	Days 6-20	137.4	136.7	131.6	124.7* (↓9)
	Days 2-20[c]	172.5	173.7	164.4	161.1 (↓7)

a Data were obtained from Table 2 on page 27 of the study report. Percent differences from controls, calculated by reviewers, are included in parentheses.
b Body weights were not subjected to statistical analysis
c Calculated by reviewers from data presented in this table
* Significantly different from controls; $p \leq 0.05$
** Significantly different from controls; $p \leq 0.01$

3. **Food consumption:** Food consumption was decreased ($p \leq 0.05$) during GD 6-7 in the ≥200 mg/kg/day females (↓9-13%). No other effect of treatment was observed on food consumption.

4. **Water consumption:** At 500 mg/kg/day, water consumption was increased ($p \leq 0.05$) during GD 8-9, 12-13, 14-15, and 18-19 (↑21-33%; Table 3). No other treatment-related effect was observed on water consumption.

Table 3. Mean maternal water consumption (g/rat/day)[a]

Interval	Dose in mg/kg bw/day (# of Dams)			
	0	80	200	500
GD 3-5	35.1	35.3	33.3	33.6
GD 12-13	39.2	41.9	42.8	52.2* (↑33)
GD 18-19	46.4	48.0	50.2	56.2* (↑21)

a Data were obtained from Table 4 on page 29 of the study report. Percent differences from controls, calculated by reviewers, are included in parentheses.
* Significantly different from controls; $p \leq 0.05$

5. **Gross pathology:** No treatment-related macroscopic findings were observed.

6. **Cesarean section data:** Cesarean section data are presented in Table 4. There were no abortions or premature deliveries. No effects of treatment were noted on numbers of litters, live

fetuses, resorptions (early, late, or complete litter), fetal body weight, litter weight, sex ratio, or post-implantation losses.

Table 4. Cesarean section observations[a]

Observation	Dose (mg/kg bw/day)			
	0	80	200	500
# Animals Assigned (Mated)	25	25	25	25
# Animals Pregnant[b]	24	23	23	23
Pregnancy Rate (%)[b]	96	92	92	92
# Nonpregnant	1	2	2	2
Maternal Wastage				
# Died	0	0	0	3
# Killed	0	0	0	2
# Died Pregnant	0	0	0	1
# Died Nonpregnant	0	0	0	0
# Aborted	0	0	0	0
# Premature Delivery	0	0	0	0
Total # Corpora Lutea[b, c]	335	316	331	273
Corpora Lutea/Dam[c]	14.0	13.7	14.4	13.7
Total # Implantations[b, c]	316	287	296	261
(Implantations/Dam)[c]	13.2	12.5	12.9	13.1
Total # Litters	24	23	23	20
Total # Live Fetuses[b]	307	273	279	253
(Live Fetuses/Dam)	12.8	11.9	12.1	12.7
Total # Dead Fetuses	NP	NP	NP	NP
(Dead Fetuses/Dam)	NP	NP	NP	NP
Total # Resorptions[b]	9	14	17	8
Early[b]	9	13	17	8
Late[b]	0	1	0	0
Total Resorptions/Dam	0.4	0.6	0.7	0.4
Early	0.4	0.6	0.7	0.4
Late	0.0	0.0	0.0	0.0
Complete Litter Resorption[d]	0	0	0	0
Mean Fetal Weight (g)	3.84	3.94	3.84	3.84
Mean Litter Weight (g)	49.02	46.56	46.64	48.62
Sex Ratio (% Male)	51.8	55.7	50.1	47.2
Preimplantation Loss (%)	5.2	8.7	9.4	4.2
Postimplantation Loss (%)	2.8	4.6	5.4	3.0

a Data were obtained from Tables 1, 5, and 6 and Appendix 5 on pages 26, 30-31, and 49-52 of the study report.
b Calculated by reviewers
c Only females with live young at Day 20 were used in calculations.
d Determined by the reviewers because # of pregnant females surviving to termination = # of litters
NP Data not provided

B. DEVELOPMENTAL TOXICITY

1. **External examination**: No external findings were noted.

2. **Visceral examination**: Selected visceral abnormalities are presented in Table 5a. There were no treatment-related visceral findings. The following malformations were observed: I) diaphragmatic hernia in one 500 mg/kg/day fetus (0.4% fetuses; 5.0% litters) compared to one concurrent control fetus (0.3% fetuses; 4.2% litters); ii) microphthalmia in two 200 mg/kg/day fetuses (0.7% fetuses; 4.3% litters) compared to one concurrent control fetus (0.3% fetuses; 4.2% litters); and iii) interventricular septal defect in one control fetus (0.3% fetuses; 4.2% litters). These findings were all considered to be incidental because they were not dose-dependent. There were no other visceral malformations.

The following anomalies were observed in the 500 mg/kg/day fetuses (0.8% fetuses; 5.0% litters) compared to 0 concurrent controls, but were considered incidental to treatment: I) subcutaneous hemorrhage of the cranium; ii) hemorrhage of the eyes/surrounding tissues; and iii) reduced thyroid. All other visceral findings were also considered to be unrelated to dose.

Table 5a. Selected visceral abnormalities [% fetuses affected (% litters affected)][a]

Observations	Dose (mg/kg bw/day)			
	0	80	200	500
Malformations				
# Fetuses (# litters) examined	307 (24)	273 (23)	279 (23)	253 (20)
Diaphragmatic hernia	0.3 (4.2)	0 (0)	0 (0)	0.4 (5.0)
Microphthalmia	0.3 (4.2)	0 (0)	0.7 (4.3)	0 (0)
Interventricular septal defect	0.3 (4.2)	0 (0)	0 (0)	0 (0)
Anomalies				
# Fetuses (# litters) examined	151 (24)	137 (23)	138 (23)	126 (20)
Subcutaneous hemorrhage, cranium	0 (0)	0 (0)	0 (0)	0.8 (5.0)
Hemorrhages, eyes/surrounding tissues	0 (0)	0 (0)	0 (0)	0.8 (5.0)
Reduced thyroid	0 (0)	0 (0)	0 (0)	0.8 (5.0)

a Data were obtained from Tables 8 and 9 on pages 33-34 of the study report. Historical control data were not provided.

3. **Skeletal examination**: Selected skeletal abnormalities are presented in Table 5b. The following malformations were observed: I) partially split sternum in one 200 mg/kg/day fetus (0.7% fetuses; 4.3% litters) compared to one concurrent control fetus (0.3% fetuses; 4.2% litters); and ii) distorted/irregular ossified ribs in one 80 mg/kg/day fetus (0.4% fetuses; 4.3% litters) compared to one concurrent control fetus (0.3% fetuses; 4.2% litters). These findings were all considered to be incidental because they were not dose-dependent. No other

malformations were observed. None of the anomalies observed could be identified as treatment-related. Increased ($p \leq 0.05$) incidence of pups with 14 ribs, a variant, was observed in the 80 (21.5% fetuses; 56.5% litters; not significant), 200 (21.7% fetuses; 73.9% litters) and 500 (23.8% fetuses; 65.0% litters) mg/kg/day groups compared to concurrent controls (10.5% fetuses; 33.3% litters). However, the fetal incidence fell within the range of historical controls (7.8-28.2%) and were not considered treatment-related. Historical control litter incidence was not provided. All other variants were unrelated to dose.

Table 5b. Selected skeletal abnormalities [% fetuses affected (% litters affected)][a]

Observations	Dose (mg/kg bw/day)			
	0	80	200	500
Malformations				
#Fetuses (litters) examined	307 (24)	273 (23)	279 (23)	253 (20)
Partially split sternum	0(0)	0 (0)	0.4 (4.3)	0 (0)
Distorted/irregularly ossified ribs	0.3 (4.2)	0.4 (4.3)	0 (0)	0 (0)
Anomalies				
#Fetuses (litters) examined	152 (24)	135 (23)	138 (23)	126 (20)
Reduced ossification of:				
one or more cranial centers	3.3 (13.0)	3.7 (13.0)	4.3 (13.0)	4.8 (15.0)
digital centers	0.7 (9.0)	2.2 (13.0)	0 (0)	2.4 (10.0)
cervical vertebral arches	0 (0)	0.7 (4.3)	0 (0)	0.8 (5.0)
Variants				
#Fetuses (litters) examined	152 (24)	135 (23)	138 (23)	126 (20)
14 ribs	10.5 (33.3)	21.5 (56.5)	21.7 (73.9)*	23.8 (65.0)*

a Data were obtained from page 22 and Tables 8, 10, and 11 on pages 33 and 35-36 of the study report.
* Significantly different from controls; $p \leq 0.05$

III. DISCUSSION and CONCLUSIONS

A. INVESTIGATORS' CONCLUSIONS: Maternal toxicity was evident at 500 mg/kg/day, manifested principally as 3 deaths, and in animals surviving to termination, as lower mean body weight gain, higher water consumption, and lower mean food intake initially. There were no obvious adverse effects on the developing conceptus at any of the dosages investigated.

B. REVIEWER COMMENTS

1. **Maternal toxicity:** There were no effects of treatment on gross pathology.

At 200 mg/kg/day, wet feces were observed on GD 8-16 in all cages. Brown perinasal staining and noisy/irregular respiration were observed sporadically in one dam. Food consumption was decreased (19%; $p \leq 0.05$) during GD 6-7. However, these minor findings were not considered adverse.

At 500 mg/kg/day, one dam was found dead on GD 9. This animal exhibited noisy respiration prior to dosing on the previous day, and post-mortem examination revealed red/brown staining of the perinasal and perioral regions, enlarged cervical lymph nodes, firm lungs with patchy congestion, and gaseous distension of the gastrointestinal tract. Also, two dams were killed for humane reasons on GD 12. These dams exhibited loss of body tone, noisy/irregular respiration, piloerection, and brown perinasal staining immediately prior to death, as well as lethargy, distended abdomen, and yellow stained urogenital region. Post-mortem examination revealed enlarged cervical lymph nodes and severe gaseous distension of the gastrointestinal tract in both animals; one animal was also found to have a roughened forestomach. All other animals survived to study termination.

Additionally at this dose, wet feces were noted on GD 7 or 8 to GD 16, post-dosing salivation was observed in 6/22 dams on GD 11/12, and noisy/irregular respiration was noted in 2/22 dams on GD 10-16 and 13-19. Body weight gains were decreased ($p \leq 0.05$) during treatment on GD 6-8 and 6-14 (↓19-41%). Body weight gains continued to be decreased ($p \leq 0.05$) to termination (GD 6-20; ↓9%) and for the overall (GD 2-20) study (↓7%; NS). Food consumption was decreased ($p \leq 0.05$) during GD 6-7 (↓13%), and water consumption was increased ($p \leq 0.05$) during GD 8-9, 12-13, 14-15, and 18-19 (↑21-33%).

The maternal LOAEL is 500 mg/kg bw/day, based on increased mortality, clinical signs of toxicity, decreased body weight gains and food consumption, and increased water consumption. The maternal NOAEL is 200 mg/kg bw/day.

2. <u>Developmental toxicity</u>

a. Deaths/Resorptions: There were no abortions, premature deliveries, or dead fetuses. No effects of treatment were noted on numbers of litters, live fetuses, resorptions (early, late, or complete litter), or on sex ratio or post-implantation losses.

b. Altered Growth: No effects of treatment were observed on fetal growth.

c. Developmental Variations: There were no treatment-related external, visceral, or skeletal variations. The only developmental variation observed that was increased ($p \leq 0.05$) was the incidence of pups with 14 ribs, a variant. This was observed in the 80, 200, and 500 mg/kg/day groups compared to concurrent controls. However, the fetal incidences fell within the range of historical controls and were not considered treatment-related.

d. Malformations: There were no treatment-related external, visceral, or skeletal malformations.

The developmental LOAEL was not observed. The developmental NOAEL is 500 mg/kg bw/day.

This study is classified **acceptable/guideline (OPPTS 870.3700a)** and satisfies the guideline requirements for a developmental study in the rat.

C. <u>STUDY DEFICIENCIES</u>: Historical control data for litter incidence of 14 ribs was not provided. This minor deficiency does not alter the conclusions of this DER. In addition, standard deviations were not presented with data means.