DATA EVALUATION RECORD

CHLOROTHALONIL

Study Type: §83-3b; Developmental Toxicity Study in Rabbits

Work Assignment No. 2-01-35 D; formerly 1-01-35 D (MRID 45710208)

Prepared for
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DATA EVALUATION RECORD

TXR#: 0052493

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

PC CODE: 081901

DP BARCODE: D301496
SUBMISSION NO.: None

TEST MATERIAL (PURITY): Chlorothalonil (Batch NF 28/01; 99.15% a.i.)

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

CITATIONS: Myers, D. (1994) Chlorothalonil: a study of the effect on pregnancy of the rabbit. Huntingdon Research Centre, Ltd., Huntingdon, Cambridgeshire, England. Laboratory Study Identification: VCM 23/930638, June 27, 1994. MRID 45710208. Unpublished.

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

EXECUTIVE SUMMARY: In an oral developmental toxicity study (MRID 45710208), Chlorothalonil (Batch NF 28/01; 99.15% a.i.) in 1.0% (w/v) aqueous methylcellulose was administered daily by gavage at a dose volume of 5 mL/kg bw to 16 female New Zealand White rabbits/group at dose levels of 0, 5, 10 or 20 mg/kg/day on gestation days (GD) 6 through 18. All does were killed on GD 29; their fetuses were removed by cesarean section and examined.

No effects of treatment were observed on mortality, clinical signs, body weights, body weight gains, food consumption, or gross pathology.

At 5 mg/kg/day, one doe died prior to dosing on GD 8. One 10 mg/kg/day female aborted her litter on GD 29; this animal exhibited cold ears during dosing, and anorexia/few feces, cold ears, red material/blood on tray paper, and no feces post-dosing. One 20 mg/kg/day aborted her litter on GD 25-26; this animal exhibited anorexia/few feces prior to dosing, anorexia/few feces, cold ears, and no feces during dosing, and anorexia/few feces, cold ears, dark eyes, no feces, fouled anogenital region, nasal exudate, soft/liquid feces, and thin appearance post-dosing. It was stated that similar findings were not observed in a preliminary developmental toxicity study in rabbits, and in view of the low incidence of animals aborting prior to terminal sacrifice, these findings are considered to be incidental to treatment.

The maternal LOAEL was not observed. The maternal NOAEL is 20 mg/kg bw/day.

No effects of treatment were noted on numbers of litters, live fetuses, resorptions (early, late, or complete litter), or post-implantation losses. Fetal growth was unaffected by treatment.

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

At 20 mg/kg/day, increased ($p \leq 0.05$) incidence of thirteen ribs, a variant, was observed (75.0% fetuses; 100% litters) compared to concurrent controls (49.2% fetuses; 93.3% litters), and reduced sternebrae, a variant, was observed (17.8% fetuses; 76.9% litters) compared to concurrent controls (8.3% fetuses; 40.0% litters). In the absence of historical control data, these findings are considered treatment-related.

The developmental LOAEL is 20 mg/kg bw/day based on increased incidence of 13th ribs and reduced sternebrae. The developmental NOAEL is 10 mg/kg bw/day.

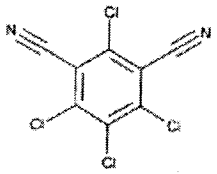
This study is classified **acceptable/guideline (OPPTS 870.3700b)**. While this study does not satisfy the current guideline requirements for a developmental toxicity study in the rabbit (approximately 20 animals/group with implantation sites; daily dosing from implantation to the day before the expected day of parturition), it does satisfy the Pesticide Assessment Guidelines, Subdivision F criteria (November, 1984) in place at the time this study was conducted. A maternal LOAEL was not observed and animals were not dosed to the limit dose (1000 mg/kg/day); however, the doses used were reasonable, based on the dose rationale provided.

COMPLIANCE: Signed and dated Data Confidentiality, GLP compliance, Flagging, and Quality Assurance statements were provided.

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% (w/v) aqueous methylcellulose

3. Test animals:

Species:	Rabbit	
Strain:	New Zealand White	
Age/body weight range on GD 0:	Approximately 16-24 weeks; 3.2-4.2 kg	
Source:	Interfauna UK, Ltd. (Huntingdon, Cambridgeshire, England)	
Housing:	Individually in stainless steel cages with perforated aluminum floor panels	
Diet:	SDS Standard Rabbit Diet SQC (Special Diet Services, Ltd., Essex, UK), *ad libitum*	
Water:	Tap water, *ad libitum*	
Environmental conditions:	**Temperature:**	18±2°C
	Humidity:	51±19%
	Air changes:	Not provided
	Photoperiod:	14 hrs light/10 hrs dark
Acclimation period:	6 days	

B. PROCEDURES AND STUDY DESIGN

1. In life dates: Start: 02/08/93 End: 03/10/93

2. Mating: Does were mated with males of proven fertility by the supplier. Once coitus was observed, each female was allowed to remain with the male for at least one hour. On successfully completing coitus, does were injected intravenously with 25 IU of Chorulon® (luteinizing hormone) to ensure ovulation took place. The day of mating was designated as gestation day (GD) 0.

3. Animal assignment: On receipt, does were randomly allocated to the groups indicated in Table 1, assigning an equal number of animals from each batch to each group and ensuring an

acceptable distribution of females mated to the same male, taking into account the derivation of the females.

Table 1. Animal assignment[a]

Dose (mg/kg bw/day)	0	5	10	20
# Females	16	16	16	16

a *Data were obtained from page 13 of the study report.*

4. **Dose selection rationale:** The dose levels summarized in Table 1 were chosen by the performing laboratory in collaboration with the Sponsor, and were based on available toxicological data, including the results of a previously performed pilot developmental toxicity study conducted by the performing laboratory (HRC Study VCM 29/28/930635; not provided). It was stated that in this study, maternal toxicity was evident at 30-40 mg/kg/day, manifested as marked anorexia and weight loss and resulting in the premature sacrifice of these animals. Initial body weight loss was apparent at 15 mg/kg/day; therefore, 20 mg/kg/day was chosen for the high dose level with some maternal toxicity without mortality anticipated. Five mg/kg/day was selected as the probable NOAEL. No other information was provided.

5. **Dosage preparation and analysis:** Stock dosing solutions were prepared fresh each day by grinding a weighed amount of test substance in a small volume of 1.0% (w/v) aqueous methylcellulose with a mortar until a smooth paste was formed. The formulation was gradually made up to volume and mixed with a high shear homogenizer. Dose formulations were resuspended within four hours of preparation and administered within 30 minutes of the commencement of resuspension. 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 was 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, 4, and 24 hours of storage (described as room temperature during the day followed by refrigeration overnight).

Results:

Homogeneity (range as % CV): 0.08-2.67%
(except 0.2 mg/mL: 42.2% at 1 hr; 18.3% at 24 hr)

Stability (range as % of time 0): 91.1-104.8%

Concentration (range as mean % nominal): 94.0-99.5%

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 6-18 at a volume of 5 mL/kg of body weight. Dosing was adjusted based on the individual body weights on Days 8, 10, and 14.

C. OBSERVATIONS

1. **Maternal observations and evaluations:** All does were checked for mortality, morbidity, and clinical signs of toxicity daily. Body weights were recorded on GDs 0, 2, 6, 8, 10, 14, 19, 23, and 29. Food consumption was reported for GDs 0-1, 2-5, 6-7, 8-9, 10-13, 14-18, 19-22, and 23-28, as group mean daily values (g/rabbit/day). On GD 29, all does were killed, dissected, and examined for congenital abnormalities and macroscopic pathological changes. The gravid uterus was excised and all fetuses were removed by cesarean section. The numbers of corpora lutea, number and distribution of all live and dead fetuses, and the number and location of resorptions (early and late) were recorded. Does killed *in extremis* or dying prior to scheduled termination were necropsied.

2. **Fetal evaluations:** All fetuses were weighed and examined for external abnormalities. Live fetuses were killed by an intrathoracic injection of pentobarbitone sodium, dissected to discern visceral abnormalities, and sexed. Fetuses were then skinned, eviscerated, and fixed in 74 OP industrial methylated spirit. After fixation, the heads were sliced through the line of the frontoparietal suture, and the brain was examined for visible abnormalities. The skeletons were cleared and stained using a modified Dawson's technique.

D. DATA ANALYSIS

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

Parameter	Statistical test
Adult body weight gain and food consumption	Testing for heterogeneity of variance was performed (test not specified), followed by parametric tests (analysis of variance followed by Williams' test) or non-parametric tests (Kruskal-Wallis analysis followed by Shirley's test) as appropriate
Mean litter data, including sex ratio and skeletal variants	Kruskal-Wallis analysis followed by Shirley's test. Where 75% or more of the values for a given variable were the same, Fisher's exact test was used
Litter distribution of fetal abnormalities	Two sample permutation test

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

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

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

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

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

3. **Historical control data:** Historical control data were not provided.

II. RESULTS

A. MATERNAL TOXICITY

1. **Mortality and clinical observations:** At 5 mg/kg/day, one doe died prior to dosing on GD 8. This animal exhibited anorexia and few feces on GD 1, and at necropsy, dark fluid in the trachea and minimal pitting of the kidneys were observed. All other animals survived to study termination. One 10 mg/kg/day female (#301) aborted her litter on GD 29; this animal exhibited cold ears during dosing, and anorexia/few feces, cold ears, red material/blood on tray paper, and no feces post-dosing. One 20 mg/kg/day doe (#402) aborted her litter on GD 25-26; this animal exhibited anorexia/few feces prior to dosing, anorexia/few feces, cold ears, and no feces during dosing, and anorexia/few feces, cold ears, dark eyes, no feces, fouled anogenital region, nasal exudate, soft/liquid feces, and thin appearance post-dosing. These findings were considered incidental. A slightly higher incidence of anorexia/few feces was noted at 20 mg/kg/day compared to controls, but it was stated that this is a common finding in rabbits and was not considered to be toxicologically significant. All other clinical signs were unrelated to dose.

2. **Body weight:** Body weight gain data are presented in Table 2. Overall (GD 0-29) body weight gains were decreased (calculated by reviewers; statistics not performed) by 25% in the 20 mg/kg/day females; however, this was primarily due to a loss of body weight during pre-treatment (GD 0-6; ↓48%). Body weight gains during treatment (GD 6-19) and post-treatment (GD 19-29) in the 20 mg/kg/day group were slightly decreased (↓9-11%); however, these losses were minor and dose-dependency was not observed. Gravid uterus weights were not presented.

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

Interval		Dose in mg/kg bw/day			
		0	5	10	20
# of Does		15	15	13	13
Pretreatment:	Days 0-6	231	134	156	119 (↓48)
Treatment:	Days 6-19	170	221	195	154 (↓9)
Post-treatment:	Days 19-29	209	183	235	187 (↓11)
Overall:	Days 0-29	610	538	586	460 (↓25)

a Body weight gains were calculated by reviewers from data obtained from Table 2 on page 26 of the study report. Percent differences from controls (calculated by reviewers) are included in parentheses.

3. **Food consumption**: At 20 mg/kg/day, food consumption was decreased (not significant [NS]) by 13% during treatment (GD 6-18; Table 3). However, food consumption was decreased both prior to treatment (GD 0-5; ↓10%) and following treatment (GD 19-28; ↓11%). Therefore, this finding was considered to be incidental to treatment. Food consumption at 5 and 10 mg/kg/day was similar to controls at all time points.

Table 3. Mean cumulative maternal food consumption (g/rabbit)[a]

Interval	Dose in mg/kg bw/day			
	0	5	10	20
# of Does	16	15	13	12-13
GD 0-5	976	926	888	874 (↓10)
GD 6-18	2004	1972	1967	1737 (↓13)
GD 19-28	1442	1360	1474	1282 (↓11)

a Data were obtained from Table 4 and Appendix 3 on pages 27 and 44-45 of the study report. Percent differences from controls (calculated by reviewers) are included in parentheses.

4. **Gross pathology**: There were no treatment-related macroscopic findings in any group. At 20 mg/kg/day, pale liver with accentuated lobular pattern and moderate bilateral cortical scarring of the kidneys were observed in one female. The female that aborted was found to have pale visceral surface of the median lobe of the liver with two white subcapsular areas, gas/liquid contents of the cecum with marked gaseous distension, rectum void of fecal pellets, and pale right kidney with minimal subcapsular cortical scarring. These findings were considered incidental.

5. **Cesarean section data**: Cesarean section data are presented in Table 4. No effects of treatment were noted on numbers of litters, live fetuses, resorptions (early, late, or complete litter), post-implantation losses, sex ratio, or fetal body weight. A slight increase in the number of late resorptions was observed at 20 mg/kg/day, but this increase was not statistically significant and was due to two does with increased late resorptions.

Table 4. Cesarean section observations[a]

Observation	Dose (mg/kg bw/day)			
	0	5	10	20
# Animals Assigned (Mated)	16	16	16	16
# Animals Pregnant[b]	15	16	14	14
Pregnancy Rate (%)[b]	93.8	100	87.5	87.5
# Nonpregnant	1	0	2	2
Maternal Wastage				
# Died	0	1	0	0
# Died Pregnant	0	1	0	0
# Died Nonpregnant	0	0	0	0
# Aborted	0	0	1	1
# Premature Delivery	0	0	0	0
Total # Corpora Lutea	172	164	145	154
Corpora Lutea/Dam	11.5	10.9	10.1	11.8
Total # Implantations	135	144	117	142
(Implantations/Dam)	9.0	9.6	8.1	9.9
Total # Litters	15	15	13	13
Total # Live Fetuses	122	134	97	110
(Live Fetuses/Dam)	8.1	8.9	7.5	8.5
Total # Dead Fetuses	NP	NP	NP	NP
(Dead Fetuses/Dam)	NP	NP	NP	NP
Total # Resorptions[b]	13	10	9	19
Early[b]	4	2	7	6
Late[b]	9	8	2	13
Total Resorptions/Dam	0.9	0.7	0.6	1.5
Early	0.3	0.1	0.5	0.5
Late	0.6	0.5	0.2	1.0
Complete Litter Resorption	0	0	0	0
Mean Fetal Weight (g)	46.3	44.0	47.0	42.2
Sex Ratio (% Male)	44.9	53.0	48.4	50.1
Preimplantation Loss (%)	22.7	13.8	18.5	16.2
Postimplantation Loss (%)	8.6	6.2	10.4	13.0

a Data were obtained from Tables 1, 5, and 6, and Appendix 4 on pages 25, 28-29, and 46-49 of the study report.
b Calculated by reviewers
NP Not provided

B. DEVELOPMENTAL TOXICITY

1. **External examination:** There were no treatment-related external findings.

2. **Visceral examination:** Visceral abnormalities are presented in Table 5a. Abnormal lobation of the liver, an anomaly, was noted in the 10 (2.1% fetuses; 15.4% litters) and 20 (3.8% fetuses; 23.1% litters) mg/kg/day groups compared to 0 concurrent controls. No other treatment-related

visceral abnormalities were observed. At 20 mg/kg/day, malformed cervicothoracic arteries (1.8% fetuses; 15.4% litters) and hydrocephaly (0.9% fetuses; 7.7% litters), both malformations, were observed compared to 0 concurrent controls. Corneal/lenticular haze/opacity of the eyes, an anomaly, was observed in the 5 (0.8% fetuses; 6.7% litters) and 20 (2.8% fetuses; 7.7% litters) mg/kg/day groups compared to 0 concurrent controls. These visceral findings were considered incidental.

3. **Skeletal examination:** Selected skeletal findings are presented in Table 5b. In the 20 mg/kg/day group, increased ($p \leq 0.05$) incidence of thirteen ribs, a variant, was observed (75.0% fetuses; 100% litters) compared to concurrent controls (49.2% fetuses; 93.3% litters); and increased ($p \leq 0.05$) incidence of reduced sternebrae, a variant, was observed (17.8% fetuses; 76.9% litters) compared to concurrent controls (8.3% fetuses; 40.0% litters). No other treatment-related skeletal findings were observed. Partially fused frontals to parietals, a malformation, was noted in a single 20 mg/kg/day fetus (0.9% fetuses; 7.7% litters) compared to 0 concurrent controls, but this finding was considered incidental. Fused/connected centers in the sternum, an anomaly, was observed in the 10 (2.1% fetuses; 15.4% litters) and 20 (1.9% fetuses; 15.4% litters) mg/kg/day groups compared to concurrent controls (0.8% fetuses; 6.7% litters), but this finding was considered minor. Unossified astragalus and enlarged fontanelles, both anomalies, were each seen in a single 20 mg/kg/day fetus (0.9% fetuses; 7.7% litters), but these findings were considered incidental. Sutural bones were noted in the 5 (3.8% fetuses; 20.0% litters) and 20 (5.7% fetuses; 23.1% litters) mg/kg/day groups compared to concurrent controls (2.5% fetuses; 13.3% litters), and irregular ossification of the cranial bones was observed in the 5 (0.8% fetuses; 6.7% litters) and 20 (2.8% fetuses; 15.4% litters) mg/kg/day groups compared to 0 concurrent controls. Both of these findings were considered minor and not dependent on dose. All other skeletal findings were also unrelated to dose.

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

Observations	Dose (mg/kg bw/day)			
	0	5	10	20
Malformations				
# Fetuses (# litters) examined	122 (15)	134 (15)	97 (13)	110 (13)
Malformed cervicothoracic arteries	0 (0)	0 (0)	0 (0)	1.8 (15.4)
Hydrocephaly	0 (0)	0 (0)	0 (0)	0.9 (7.7)
Anomalies				
# Fetuses (# litters) examined	120 (15)	133 (15)	96 (13)	106 (13)
Liver - abnormal lobation	0 (0)	0 (0)	2.1 (15.4)	3.8 (23.1)
Eyes - corneal/lenticular haze/opacity	0 (0)	0.8 (6.7)	0 (0)	2.8 (7.7)

a Data were obtained from Tables 8 and 9 on pages 31-32 of the study report.

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

Observations	Dose (mg/kg bw/day)			
	0	5	10	20
Malformations				
#Fetuses (litters) examined	122 (15)	134 (15)	97 (13)	110 (13)
Partially fused frontals to parietals	0 (0)	0 (0)	0 (0)	0.9 (7.7)
Anomalies				
# Fetuses (litters) examined	120 (15)	133 (15)	96 (13)	106 (13)
Sternum - fused/connected centers	0.8 (6.7)	0 (0)	2.1 (15.4)	1.9 (15.4)
Unossified astragalus	0 (0)	0 (0)	0 (0)	0.9 (7.7)
Enlarged fontanelles	0 (0)	0 (0)	0 (0)	0.9 (7.7)
Sutural bones	2.5 (13.3)	3.8 (20.0)	0 (0)	5.7 (23.1)
Irregular ossification of cranial bones	0 (0)	0.8 (6.7)	0 (0)	2.8 (15.4)
Variations				
# Fetuses (litters) examined	120 (15)	133 (15)	96 (13)	106 (13)
13 Ribs (% affected)	49.2 (93.3)	52.5 (93.3)	46.4 (84.6)	75.0* (100)
Reduced sternebrae	8.3 (40.0)	5.4 (26.7)	8.2 (53.8)	17.8* (76.9)

a Data were obtained from Tables 8, 10, and 11 and Appendix 8 on pages 31, 33-34, and 63-64 of the study report.

* Significantly different from controls; $p \leq 0.05$

III. DISCUSSION and CONCLUSIONS

A. INVESTIGATORS' CONCLUSIONS: The slight mean body weight loss during the first two days of dosing at 20 mg/kg/day was considered to be indicative of a threshold dose for maternal toxicity. A greater proportion of animals showed body weight loss during this period when compared to other groups. There were also two litters at this dosage with mean fetal weights less than 30 g and another two litters with a slightly higher number of embryonic deaths relative to the number of implantations. Although there was no conclusive maternal toxicity, there was evidence to suggest that 20 mg/kg/day was a threshold dose and that occasional, more susceptible, animals were giving a greater response. Some minor skeletal changes, such as a higher number of fetuses with 13 ribs, were not entirely unexpected at this dose.

B. REVIEWER COMMENTS

1. Maternal toxicity: No effects of treatment were observed on mortality, clinical signs, body weights, body weight gains, food consumption, or gross pathology.

At 5 mg/kg/day, one doe died prior to dosing on GD 8. This animal exhibited anorexia and few feces on GD 1, and at necropsy, dark fluid in the trachea and minimal pitting of the kidneys were observed. One 10 mg/kg/day female aborted her litter on GD 29; this animal exhibited cold ears during dosing, and anorexia/few feces, cold ears, red material/blood on tray paper, and no feces

post-dosing. One 20 mg/kg/day aborted her litter on GD 25-26; this animal exhibited anorexia/few feces prior to dosing, anorexia/few feces, cold ears, and no feces during dosing, and anorexia/few feces, cold ears, dark eyes, no feces, fouled anogenital region, nasal exudate, soft/liquid feces, and thin appearance post-dosing. It was stated that similar findings were not observed in a preliminary developmental toxicity study in rabbits, and in view of the low incidence of animals aborting prior to terminal sacrifice, these findings are considered to be incidental to treatment.

The maternal LOAEL was not observed. The maternal NOAEL is 20 mg/kg bw/day.

2. <u>Developmental toxicity</u>

a. Deaths/Resorptions: No effects of treatment were noted on numbers of litters, live fetuses, resorptions (early, late, or complete litter), or post-implantation losses. A slight increase in the number of late resorptions was observed at 20 mg/kg/day, but this increase was not statistically significant and was due to two does with increased late resorptions.

b. Altered Growth: Fetal growth was unaffected by treatment.

c. Developmental Variations: At 20 mg/kg/day, increased ($p \leq 0.05$) incidence of thirteen ribs, a variant, was observed (75.0% fetuses; 100% litters) compared to concurrent controls (49.2% fetuses; 93.3% litters), and increased ($p \leq 0.05$) incidence of reduced sternebrae, a variant, was observed (17.8% fetuses; 76.9% litters) compared to concurrent controls (8.3% fetuses; 40.0% litters). In the absence of historical control data, these findings are considered treatment-related. There were no other treatment-related external, visceral, or skeletal variations. Abnormal lobation of the liver, an anomaly, was noted in the 10 (2.1% fetuses; 15.4% litters) and 20 (3.8% fetuses; 23.1% litters) mg/kg/day groups compared to 0 concurrent controls. However, this finding was not statistically significant, and was not considered to be adverse.

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

The developmental LOAEL is 20 mg/kg bw/day based on increased incidence of 13 ribs and reduced sternebrae. The developmental NOAEL is 10 mg/kg bw/day.

This study is classified **acceptable/guideline (OPPTS 870.3700b)**. While this study does not satisfy the current guideline requirements for a developmental toxicity study in the rabbit (approximately 20 animals/group with implantation sites; 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. A maternal LOAEL was not observed and animals were not dosed to the limit dose (1000 mg/kg/day); however, the doses used were reasonable, based on the dose rationale provided.

C. <u>STUDY DEFICIENCIES</u>: The following deficiencies were noted, but do not alter the conclusions of this DER:

- Standard deviations were not presented with data means.
- Animals were not dosed to the limit dose (1000 mg/kg/day).
- Historical control data were not provided for fetal external, visceral, and skeletal findings.

- Dosing time frame GD 6-18 (old guidelines) instead of 6-28 (new guidelines).
- Only 16 rabbits/dose were used (old guidelines) vs 20 rabbits/dose (new guidelines).

MRID 45710208

Corpora lutea

Dose	0	5	10	20
	11	7	11	16
	13	14	10	15
	10	13	11	11
	15	14	7	13
	11	11	11	12
	11	12	13	11
	16	7	12	9
	11	12	11	9
	14	11	6	11
	10	11	10	12
	5	9	11	10
	10	15	9	12
	13	5	9	13
	12	12	14	
	10	11		
Total	172	164	145	154

Implants

Dose	0	5	10	20
	11	7	9	14
	11	14	7	12
	7	11	11	7
	15	14	7	13
	9	7	10	12
	11	11	11	4
	4	5	6	9
	11	12	10	9
	13	5	5	7
	10	10	9	10
	1	9	2	10
	7	14	9	9
	11	3	9	13
	6	11	12	13
	8	11		
Total	135	144	117	142

Live young

Dose	0	5	10	20
	9	7	7	9
	11	14	7	7
	7	11	11	6
	14	14	6	12
	7	7	9	11
	11	10	11	4
	4	5	5	9
	10	10	10	9
	10	5	5	6
	8	6	9	9
	1	8	1	10
	7	13	8	7
	11	3	8	11
	5	11	0	0
	7	10		
Total	122	134	97	110