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DATA EVALUATION RECORD

MEVINPHOS

Study Type: §83-3[b]; Teratology in Rabbits with Revisions

Work Assignment No. 1-01-15A (MRID's 41823801 and 42422201)

Prepared for

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Disclaimer

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

The maternal LOAEL is 0.5 mg/kg/day, based on decreased plasma cholinesterase activity. The maternal NOAEL is 0.05 mg/kg/day.

There were no treatment-related effects on various parameters (pre- and post-implantation losses, number of fetuses per litter), fetal deaths, fetal weight, or developmental parameters.

The developmental LOAEL was not observed. The developmental NOAEL is 1.5 mg/kg/day, the highest dose tested.

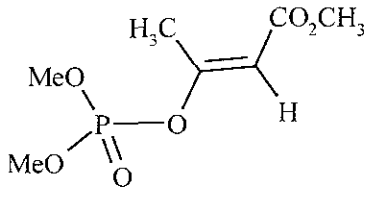
This developmental toxicity study is classified **acceptable /guideline (§83-3[b]; OPPTS 870.3700)** and does satisfy the guideline requirement for a developmental toxicity study in the rabbit.

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

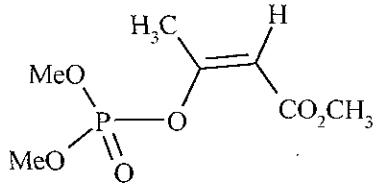
I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: Mevinphos
   Description: Colorless liquid
   Lot/Batch #: I
   Purity: 89.57% a.i., nominally 74.48% alpha (α) isomer and 15.09% beta (β) isomer
   Storage: Refrigeration
   CAS #: 7786-34-7
   Structure:



Mevinphos - alpha



Mevinphos - beta

2. Vehicle: Reverse osmosis water

3. Test animals: Species: Rabbit
   Strain: New Zealand White
   Age at mating: Approximately 7 months
   Weight at mating: 3501-5611 g
   Source: Hazleton Research Products, Inc., Denver, PA
   Housing: Individually in suspended stainless steel cages with indirect bedding
   Diet: Agway PRO LAB Special R.C.A. Rabbit Diet, ad libitum, (Agway Inc., Syracuse, NY)
   Water: Tap water, ad libitum
   Environmental conditions:
   Temperature: 65-70°F
   Humidity: 40-60%
   Air changes: Not reported
   Photoperiod: 12 hrs dark/12 hrs light

Acclimation period (P): 42 days

B. PROCEDURES AND STUDY DESIGN

1. In life dates - start: 1/22/90 end: 3/1/90.

2. Mating: Females were artificially inseminated using semen obtained from stock males of the same strain. The day artificial insemination was performed was designated day 0 of gestation.

3. Animal assignment: Animals were randomly assigned (stratified by weight) to dose groups as indicated in Table 1.

Table 1. Animal assignment

Test Group	Dose (mg/kg/day)	Number of Females
Control	0	20
Low	0.05	20
Mid	0.5	20
High	1.5	20

4. Dose selection rationale: Dose selection was based on a mevinphos teratology range finding study. Inseminated rabbits (8 females/dose) were dosed once daily by oral gavage during gestation days 7-19 at doses of 0, 0.05, 0.5, 1.5, 2.0, and 4.0 mg/kg/day. Ten animals died during the study: 1 from the 1.5 mg/kg dose level, 3 at the 2.0 mg/kg level, and 6 in the 4.0 mg/kg group. The remaining two females in the high-dose group were sacrificed prior to scheduled cesarean section (gestation day 29) for humane reasons. No adverse treatment-related effects were observed during treatment or at necropsy in animals surviving until gestation day 29. When compared to concurrent controls, maternal body weight gains decreased approximately 14% and 25% during treatment in animals dosed at 2.0 and 1.5 mg/kg, respectively; moderate reductions in food consumption were also observed at these dose levels. Maternal plasma cholinesterase levels were reduced 10.8%, 45.8%, and 19.9% in females receiving 0.5, 1.5, and 2.0 mg/kg, respectively; erythrocyte cholinesterase reductions were minimal in these groups. No toxicologically significant effects were observed regarding cesarean section data, mean fetal body weights, or mean fetal crown-rump lengths; no malformations or variations were noted during external fetal examinations.

Based on the results of this range finding study, 1.5 mg/kg/day was selected as the high-dose for the subsequent full developmental toxicity study. Low- and mid-level doses

chosen were 0.05 and 0.5 mg/kg/day.

5. Dosage preparation and analysis - Dose solutions were prepared twice weekly by mixing the appropriate amount of test substance with reverse osmosis water; solutions were stored under refrigeration. Aliquots of dose solutions were warmed to room temperature and thoroughly mixed prior to dosing. For homogenization/concentration analyses, samples were collected weekly (3 times total) from each dose level and examined in duplicate. Stability analyses were performed at 1, 160, and 6000 ppm prior to initiation of the study; samples were stored under refrigeration for 6-7 days.

   Results - Homogenization/concentration analyses: low-dose, 86.4-107.2% of nominal; mid-dose, 92.2-103.6% of nominal; high-dose, 95.9-98.7% of nominal.

   Stability Analyses: Pre-dosing concentrations were as follows: low-dose, 111-126% of nominal; mid-dose, 108.1-111.9% of nominal; high-dose, 96.8-101.6% of nominal.

   The analytical data indicated that the mixing procedure was adequate and that the variance between nominal and actual dosage to the study animals was acceptable.

6. Dosage administration: All doses were administered once daily by gavage, on gestation days 7 through 19, in a volume of 1.0 ml/kg. Dosing was based on the most recent body weights. Control animals received the carrier, reverse osmosis water, only.

C. OBSERVATIONS

1. Maternal observations and evaluations - The animals were checked for mortality twice daily during the treatment interval and at least once daily at other times during the study. Moribund females or those showing signs of abortion or premature delivery were sacrificed upon observation. Clinical observations were made once daily. Body weight data were recorded prior to selection and on gestational days 0, 7, 10, 13, 16, 19, 22, 25, and 29; food consumption data were measured concurrently. Dams were sacrificed on day 29 of gestation. Examinations at sacrifice consisted of a gross exam of the thoracic and abdominal cavities. The reproductive tract was removed, examined, and the following were recorded:
   - gravid uterine weight with ovaries attached
   - number and distribution of implantation sites
   - number of corpora lutea in each ovary
   - number and distribution of fetuses (live and dead)
   - number and distribution of resorptions

   The uteri of all apparently non-pregnant females were stained to confirm pregnancy status.

   On gestational day 19, blood was obtained from each animal approximately 3 hours post-dosing to measure cholinesterase levels in plasma and erythrocytes; however, several

blood samples were taken up to 30 minutes earlier or up to approximately 1 hour later than this 3 hour period. It was also necessary to re-bleed several animals due to clotting of the original samples, and these samples were collected approximately 1 hour and 42 minutes later than the specified 3 hours. The cholinesterase methodology was not specified in the definitive study, however in the range-finding study the method was hydrolysis of acetylthiochololine and reaction with Ellman's Reagent.

2. Fetal evaluations - Each fetus was weighed, sexed, and examined for external abnormalities. Fetal crown-rump lengths were measured for all live and dead fetuses. Visceral exams were performed on all fetuses from each litter. Following alizarin red staining, skeletal examinations were performed on all fetuses. On the day of visceral examination, approximately half of each litter was evaluated for the presence of brain (ventricular) abnormalities. Two premature litters, one each in the low- and mid-dose groups, did not receive skeletal examinations.

D. DATA ANALYSIS

1. Statistical analyses: All data collected were subjected to routine appropriate statistical procedures, such as Bartlett's test, Kruskal-Wallis (non-parametric) test, Fisher's exact test and Chi-square analysis.

2. Indices: Pre- and post-implantation indices were calculated from cesarean section records of animals in the study. Formulations for calculation were not provided.

3. Historical control data: Some historical control data were provided to allow comparison with concurrent controls.

II. RESULTS

A. MATERNAL TOXICITY

1. Mortality and clinical observations: Clinical signs observed in all dose groups including controls consisted of poor food consumption, staining of the ano-genital skin/fur, and reduced stool; all were considered unrelated to treatment. Treatment-related effects were found in a single high-dose female and included hypothermia, ataxia, hyperpnea, and clear oral discharge on gestation day 18.

   Two high-dose females were found dead on gestation day 18. Of these deaths, one was the result of a gavage accident based on postmortem evaluation; the second appeared to be treatment-related as indicated by the lack of findings in the postmortem examination to suggest a gavage accident.

2. Body weight: Body weight data are summarized in Tables 2a and 2b. Mean body weights were comparable between treated and control groups during the study (Table 2a).

At 1.5 mg/kg/day, body weight gains were reduced (not statistically significant) compared to controls during pre-treatment (↓25%, days 0-7), initial treatment (↓291%, days 7-10), overall treatment (↓173%, days 7-19), and post-treatment (↓96%, days 19-22) intervals (Table 2b). Mean overall body weight gains when corrected for gravid uterine weight were reduced in the high-dose females (↓174%, days 0-29, $p \leq 0.05$).

Table 2a. Maternal body weights (g) [a]

Interval	Dose in mg/kg/day (# of Dams)			
	0 (19)	0.05 (17)	0.5 (16)	1.5 (17)
Pretreatment:				
Day 0	4436.7±528.3	4468.1±502.9	4469.9±421.5	4446.3±400.7
Day 7	4528.5±516.6	4558.4±485.9	4538.3±420.2	4515.1±367.3
Treatment:				
Day 10	4513.7±509.9	4555.9±505.9	4528.9±419.1	4457.2±381.4
Day 16	4576.7±503.1	4634.5±487.8	4612.2±502.9	4474.4±486.6
Day 19	4572.6±511.9	4670.5±473.0	4611.9±502.2	4482.9±442.4
Post-treatment:				
Day 22	4618.8±531.4	4705.8±498.6	4654.8±553.0	4484.8±419.7
Day 29	4632.0±515.6	4731.9±518.8 (16)	4796.1±390.4 (15)	4490.5±417.6 (16)

a Data extracted from the study report Table 2, page 39.

Table 2b. Maternal body weight gain (g) [a]

Interval	Dose in mg/kg/day			
	0 (19) [b]	0.05 (17)	0.5 (16)	1.5 (17)
Pretreatment: Days 0-7	91.7±65.1	90.4±66.4	68.4±113.7	68.8±135.9 (25%)[c]
Treatment: Days 7-10	-14.8±56.6	-2.5±68.5	-9.4±71.8	-57.9±71.3 (291%)
Treatment: Days 13-16	29.6±71.4	49.2±55.0	50.9±87.6	-21.1±203.6
Treatment: Days 16-19	-4.1±76.1	35.9±54.6	-0.3±90.9	8.5±218.2
Overall treatment: Days 7-19	44.1±136.3	112.1±100.2	73.6±166.4	-32.2±205.0 (173%)
Posttreatment: Days 19-22	46.2±86.7	35.3±73.4	42.9±75.4	1.9±72.8 (96%)
Posttreatment: Days 25-29	-10.0±89.4	-4.1±137.0 (16)	-1.7±100.4 (15)	-14.9±105.3 (16)
Corrected body weight gain[d]: Days 0-29	-129.0±202.8 **324.3**	-54.7±259.8 (15) **334.2**	-235.4±186.3 (15) **499.9***	-354.1±303.0* (16) (174%) **428.6**

a Data extracted from the study report Table 2, page 39 and MRID 42422201, Table 3, page 6.
b Number of dams listed parenthetically.
c Percent decrease in comparison to control value.
d Corrected for gravid uterine weight; gravid uterine weight (g) presented in bold.
* Significantly different from controls at $p \leq 0.05$.

3. Food consumption - Food consumption data are presented in Table 3 below. At 1.5 mg/kg/day, decreases in food consumption were noted during treatment (↓9-17%, days 7 - 19) and post-treatment (20-25%, days 19-29). There were no statistically significant differences. Food consumption for high-dose animals was comparable to concurrent controls for the overall study interval (days 0-29) as food consumption in the controls was also decreasing throughout the study. Food consumption was comparable to the controls at 0.05 and 0.5 mg/kg/day throughout the study.

Table 3. Maternal food consumption (g/rabbit). [a]

Interval	Dose in mg/kg/day			
	0	0.05	0.5	1.5
Pretreatment: [b] Days 0-7	1229.8±206.3 (18)	1212.5±196.9 (16)	1199.6±234.7 (16)	1256.5±161.1 (13)
Treatment: Days 7-10	586.2±115.2 (18)	582.7±105.0 (17)	585.6±83.5 (12)	485.2±200.5 (13)
Treatment: Days 13-16	528.2±125.4 (18)	580.9±101.1 (17)	518.1±285.0 (15)	480.7±225.7 (17)
Treatment: Days 16-19	506.2±176.8 (19)	584.2±110.4 (17)	494.1±210.5 (16)	450.6±253.9 (15)
Posttreatment: Days 19-22	512.1±141.3 (17)	535.3±152.3 (16)	470.5±189.6 (15)	386.4±247.7 (16)
Posttreatment: Days 25-29	483.0±227.8 (17)	531.6±241.9 (15)	464.4±164.6 (15)	385.2±269.4 (14)
Overall: Days 0-29	4909.9±729.0 (15)	5222.6±796.5 (13)	4825.8±737.6 (9)	4932.8±781.1 (8)

a Data extracted from the study report, Table 4, page 41.
b Number of dams/group presented parenthetically; because of excessive food spillage, consumption could not be measured for all dams at each interval.

4. Gross pathology - There were no treatment-related gross pathologic findings upon necropsy.

5. Serum chemistry - When compared to concurrent controls, dose-dependent decreases of plasma and erythrocyte cholinesterase levels were observed at all dose levels (Table 4). Plasma cholinesterase levels were significantly ($p \leq 0.01$) lower than controls at the mid- (↓33%) and high- (↓47%) dose levels; erythrocyte cholinesterase levels were lower ($p \leq 0.05$ or 0.01) than controls at the low- (↓6%), mid- (↓13%), and high- (↓18%) doses.

Table 4. Maternal serum cholinesterase (IU/L). [a]

Observation	Dose in mg/kg/day (# of Dams)			
	0 (19)	0.05 (18)	0.5 (20)	1.5 (17)
Plasma cholinesterase	586±141	563±112 (4%)[b]	393±75** (33%)	309±69** (47%)
Erythrocyte cholinesterase	6082±471	5716±420* (6%)	5307±395** (13%)	4960±369** (18%)

a Data extracted from the study report, Table 5, page 43.
b Percent decrease from control value.
* Significantly different from controls at $p \leq 0.05$.
** Significantly different from controls at $p \leq 0.01$.

6. Cesarean section data - Cesarean section observations are presented in Table 5. The number of implantations, resorptions per dam, percent male, and the extent of post-implantation losses were similar between control and treated groups. In addition, fetal weights were unaffected by treatment at all dose levels. In the study report, mean data were presented in Table 7 (page 46) for the following parameters: total live fetuses, male fetuses, female fetuses, resorptions, implantations, corpora lutea, total dead fetuses, preimplantation and postimplantation loss, fetal weights and fetal crown-rump length. The mean parameters were based on the following number of litters in the control, 0.05, 0.5 and 1.5 mg/kg/day doses, respectively: 18, 17, 16 and 16. However, page 25 of the study report states that the number of fetuses (litters) examined was 90(15), 91(16), 118(16) and 106(16). Appendix F (pages 79-81), Individual Uterine Implantation Data, shows that the control and 0.05 mg/kg/day groups had 3 and 1 litters, respectively, with no live fetuses. This accounts for the difference in numbers.

Table 5. Cesarean section observations [a]

Observation	Dose (mg/kg/day)			
	0.00	0.05	0.5	1.5
# Animals Assigned (Mated)	20	20	20	20
# Animals Pregnant Pregnancy Rate (%) [b]	19 (95)	17 (85)	16 (80)	18 (90)
# Nonpregnant [b]	1	3	4	2
# Total Dams Died [b] # Died Pregnant [b] # Died Nonpregnant [b] # Aborted [b] # Premature Delivery [b]	10.00	1.00	1.00	21,110.00
Total # Corpora Lutea [b] Corpora Lutea/Dam	198 11.00±4.72	199 11.71±3.22	199 12.44±3.42	219 13.69±3.84
Total # Implantations [b] Implantations/Dam	104 5.78±3.62	100 5.88±3.79	128 8.00±2.31	110 7.50±3.01
Total # Litters Examined	18	17	16	16
Total # Live Fetuses Live Fetuses/Dam	90 5.00±3.53	91[c] 5.35±3.84	118 7.38±2.45	106 6.63±2.53
Total # Dead Fetuses [b] Dead Fetuses/Dam	0.00	0.00	3 0.19±0.75	0.00
Total # Resorptions [b] Early Late Resorptions/Dam Early Late Litters with Total Resorptions [b]	10 NR NR 0.56±0.70 NR NR 3	8 NR NR 0.47±0.87 NR NR 1	7 NR NR 0.44±0.63 NR NR 0	14 NR NR 0.88±1.15 NR NR 0
Mean Fetal Weight (g) [b] Males Females	44.06±7.91 45.85±7.55 42.89±8.04	45.19±8.35 45.47±6.06 44.86±10.69	45.75±6.07 47.56±6.21 43.82±5.31	44.36±7.56 44.35±8.33 44.38±6.59
Sex Ratio (% Male) [b]	40.0	58.2	51.7	52.3
Preimplantation Loss (%)	42.2±28.8	50.8±27.1	32.9±19.5	42.5±23.1
Postimplantation Loss (%)	23.7±36.3	13.7±27.2	8.0±11.0	10.6±12.5

a Data extracted from the study report, pages 25, Tables 7 and 8, pages 46 through 47, and Appendices F and G, pages 79 through 84.
b Calculated by reviewer.
c Includes one litter of 8 males and 3 females which delivered prematurely; doe was euthanized prior to GD 29.
NR Not reported

B. DEVELOPMENTAL TOXICITY Fetal examinations included external, visceral, and skeletal observations at necropsy.

1. External examination - There were no malformations or variations detected in the control or treated groups. Crown-rump lengths are shown in Table 6a.

Table 6a. External examinations [a]

Observations	Dose (mg/kg/day)			
	0	0.05	0.5	1.5
#Fetuses (#litters) examined	90 (15)	80 (16)	112 (16)	97 (16)
Crown-rump lengths (cm)				
Males	9.43±0.59	9.37±0.51	9.50±0.47	9.44±0.71
Females	9.19±0.63	9.32±0.98	9.32±0.46	9.36±0.69

a Data extracted from the study report Table 9, page 48.

2. Visceral examination - There were no treatment-related visceral variations or malformations observed at any dose level. The most common findings are presented in Table 6b. Statistically significant variations (on a per fetal basis) included an increased incidence of cardiovascular accessory vessels at the high-dose (↑196%, $p<0.01$) when compared to concurrent controls. Increased incidence of cardiovascular accessory vessels appeared in a dose-dependent manner on a litter basis; however, the toxicological significance of this finding is not understood.

Table 6b. Visceral examinations [a]

Observations	Dose (mg/kg/day)			
	0	0.05	0.5	1.5
#Fetuses (#litters) examined	90 (15)	91 (16)	118 (16)	106 (16)
Malformations				
Cardiovascular [b] Retro-esophageal right subclavian	0 (0)	1.1 (6.3)	0 (0)	0 (0)
Diaphragm Extremely thin and transparent	0 (0) **0**	0 (0) **0**	0.85 (6.3) **0.88**	0 (0) **0**
Cardiovascular Ventricular septal defect	0 (0) **0**	0 (0) **0**	0 (0) **0**	0.94 (6.3) **0.81**
Variations				
Cardiovascular Accessory vessels [c]	6.7 (20.0) **6.6**	16.5 (37.5) **17.2**	11.0 (43.8) **9.8**	19.8** (56.3) **19.5**
Cardiovascular Other vessel variations [c]	11.1 (33.3) **8.7**	3.3 (18.8) **3.1**	2.5* (18.8) **2.4**	4.7 (31.3) **4.6**
Testes Immature accessory sex tissue	1.1 (6.7) **1.7**	1.1 (6.3) **1.3**	1.7 (6.3) **2.5**	1.9 (6.3) **1.4**

a Data extracted from the study report, Table 10, pages 49 through 52.
b For individual observations, data are presented as % fetal incidence, (%litter incidence), and **% affected fetuses/litter**. All were calculated by reviewer.
c Dose-response trend, $p<0.05$ by Armitage Test.
* Significantly different from controls at $p<0.05$.
** Significantly different from controls at $p<0.01$.

3. Skeletal examination - The most common skeletal findings are presented in Table 6c. There were no treatment-related skeletal malformations observed at any dose level. At the high-dose, an increased incidence of hypoplastic hyoid was identified as a dose-response trend ($p<0.05$) by Armitage test; however, this finding occurred in a single litter and is within the historical control ranges (fetal incidence 5.7% vs historical control range 4.9-8.3%; litter incidence 6.3% vs control range 13.3-37.5%), and therefore, is not considered to be treatment-related. An increased incidence of unossified bones of the forepaw observed in the high dose group (↑80% vs controls, fetal incidence) was noted as a dose-response trend ($p<0.01$) by Armitage test; however, this finding was also within historical control ranges (fetal incidence 16.0% vs control range 3.6-35.1%; litter incidence 31.3% vs control range 18.8-80.0%) and is not considered treatment-related.

Table 6c. Skeletal examinations [a]

Observations	Dose (mg/kg/day)				
	0	0.05	0.5	1.5	Historical Control Ranges
#Fetuses (#litters) examined	90 (15)	80 (15)	112 (15)	106 (16)	698 (123)
Malformations					
Sternebrae Malformed/fused	0 (0) **0**	5.0 (20.0) **5.4**	0 (0) **0**	1.9 (6.3) **2.5**	NR
Variations					
Hyoid [c] Hypoplastic	0 (0) **0**	1.3 (6.7) **0.6**	0.89 (6.7) **0.7**	5.7 (6.3) **3.4**	4.9-8.3 (13.3-37.5)
Forepaw [d] Unossified	8.9 (33.3) **11.5**	10.0 (26.7) **10.5**	5.4 (26.7) **4.7**	16.0 (31.3) **13.9**	3.6-35.1 (18.8-80.0)
Sternebrae Unossified	21.1 (53.3) **18.1**	11.3 (26.7) **7.3**	7.1** (26.7) **6.1**	9.4 (31.3) **6.7**	NR

a Data extracted from the study report Table 10, pages 49 through 52 and MRID 42422201 page 8.
b For individual observations, data are presented as % fetal incidence, (%litter incidence), and **% affected fetuses/litter**. All were calculated by reviewer.
c Dose-response trend, $p<0.05$ by Armitage Test.
d Dose-response trend, $p<0.01$ by Armitage Test.
** Significantly different from controls at $p<0.01$.
Historical control data failed to report % affected fetuses/litter observations.
NR Not reported

III. DISCUSSION

A. INVESTIGATORS' CONCLUSIONS The study report concluded that gavage administration of mevinphos (89.57% a.i.) at 1.5 mg/kg/day to pregnant rabbits during gestation days 7-19 was associated with mortality, clinical signs of toxicity, and reduced body weight gains. Biologically significant maternal plasma and erythrocyte cholinesterase inhibition was observed at 0.5 and 1.5 mg/kg/day compared with controls. The maternal LOAEL is 0.5 mg/kg/day. The maternal NOAEL is 0.05 mg/kg/day.

No treatment-related malformations were noted. There were no effects on fetal body weights or crown-rump lengths at any dose level. Fetal variations were observed in all four dose groups; accessory vessels (accessory left subclavian and/or intercostal artery) was the most frequently observed variation, but this observation is not considered biologically significant. Increased incidences of hypoplastic hyoid and unossified forepaw in the high-dose group were observed; however these findings were not supported by fetal body weight data and are within the historical control ranges, and therefore, are not considered biologically significant.

The developmental LOAEL was not established and the NOAEL is 1.5 mg/kg/day.

B. REVIEWER'S DISCUSSION

1. MATERNAL TOXICITY: Mevinphos (89.57% a.i.) was administered by gavage at 0, 0.05, 0.5, or 1.5 mg/kg/day to artificially inseminated rabbits (20 females/dose) on days 7-19 of gestation. At the high-dose level, maternal toxicity was characterized by one treatment-related death and clinical observations including hypothermia, ataxia, hyperpnea, and clear oral discharge on gestation day 18 in a single dam. At 1.5 mg/kg/day, body weight gains were reduced (not statistically significant) compared to controls during pre-treatment (↓25%, days 0-7), initial treatment (↓291%, days 7-10), overall treatment (↓173%, days 7-19), and post-treatment (↓96%, days 19-22) intervals. Mean overall body weight gains when corrected for gravid uterine weight were reduced in the high-dose females (↓174%, days 0-29, $p \leq 0.05$).

   Plasma cholinesterase levels were significantly ($p \leq 0.01$) lower than controls at the mid- (↓33%) and high- (↓47%) dose levels; erythrocyte cholinesterase levels were lower ($p \leq 0.05$ or 0.01) than controls at the low- (↓6%), mid- (↓13%), and high- (↓18%) doses. The observed inhibition of erythrocyte cholinesterase is not considered toxicologically significant due to the magnitude of the differences between control and treated groups.

   There were no treatment-related effects in food consumption, gross pathologic findings, or cesarean section parameters at any dose level.

   Maternal NOAEL = 0.05 mg/kg/day
   Maternal LOAEL = 0.5 mg/kg/day, based on reduced plasma cholinesterase activity.

2. DEVELOPMENTAL TOXICITY: There were no treatment-related developmental effects noted at any dose level.

   a. Deaths/Resorptions: The numbers of resorptions/dam and viable fetuses/dam for the treatment groups were not significantly different from the concurrent controls.
   b. Altered Growth: There were no treatment-related changes in fetal body weights at any dose level.
   c. Developmental Variations: There were no treatment-related developmental variations noted at any dose level.
   d. Malformations: There were no treatment-related developmental malformations noted at any dose level.

   Developmental NOAEL = 1.5 mg/kg/day, the highest dose tested
   Developmental LOAEL = Not observed

C. STUDY DEFICIENCIES - The following deficiencies were noted but will not affect the conclusions of the report:

- incidence of mortality of mated females was not reported in a summary table
- number of mated females that were pregnant was not reported in a summary table
- total numbers of corpora lutea, implantations, resorptions, dead fetuses, and percent male fetuses were not reported in a summary table