UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

007161

MAY - 8 1989

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

TO: Dennis Edwards, PM # 12
Insecticides/Rodenticide Branch
Registration Division H75005C

THRU: M. Ioannou, Ph.D., Acting Head
Rev. Sec. # I
HFASB/HED H7509C

THRU: Marcia Van Gemert, Ph.D.
Chief
HFASB/HED H7509C

FROM: D. Ritter, Toxicologist
Rev. Sec# I
HFASB/HED H7509C

Action Requested: Azinphs-methyl - Review a developmental toxicity study in rabbits.

Registrant: Mobay Corporation, Kansas City, MO.

Caswell #: 374.

TOX Project #:8-1064.

Mobay submitted the following study in response to the Azinphos-methyl Guidance document:

A Teratology Study in the Rabbit with Azinphos-methyl (Guthion Technical). Study # MTD0070, Miles Laboratory, Inc., Mobay # 97406. G. R. Clemens, et al.

The study was reviewed by Patricia A. Turck of Dynamac Corporation under Task # 1-44, and the DER is attached.

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Summary:

Gravid rabbits were assigned, 20 each, to dose-groups receiving 0, 1.0, 2.5 or 6.0 mg/kg/day of test material by oral intubation on days 6 through 18 of gestation. Does were observed for toxic effects. On gestation day 28 the does were killed and uterine contents evaluated for developmental toxicity.

The maternal toxicity NOEL, as evidenced by cholinesterase inhibition and clinical signs, was determined to be 1.0 mg/kg/day. The LOEL for this effect was determined to be 2.5 mg/kg/day.

A dose-related increase was observed in the incidence of fetuses and litters affected with lumbar and sacral vertebrae abnormalities (missing or extra arch; missing or extra centra) in the low- and mid-dose groups but not in the high-dose group. Additional historical control data are required before the developmental toxicity of azinphos-methyl can be assessed.

CLASSIFICATION: Core supplementary data.

Tox Chem No. 374 - Azinphos-Methyl File Last Updated _____ Current Date _____

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Pathology - Rabbit; Toxicol. Dep., Miles Inc. Elkhart, IN.; MTD0070; 6-27-88	Guthion (87.7% ai)	407139-01	Maternal LEL = 2.5 mg/kg/day (based on plasma and RBC cholinesterase inhibition) Maternal NOEL = 1.0 mg/kg/day Developmental NOEL and LEL have not been established (historical control data are required).		Supplementary

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EPA: 68D80056
DYNAMAC No.: 144-A
TASK No.: 1-44A
April 24, 1989

DATA EVALUATION RECORD

AZINPHOS-METHYL

Developmental Toxicity Study in Rabbits

STUDY IDENTIFICATION: Clemens, G. R., J. J. Bare and R. E. Hartnagel. A teratology study in the rabbit with azinphos-methyl (Guthion® Technical). (Unpublished study No. MTD0070, conducted by Miles, Inc., Elkhart, IN for Mobay Corporation, Inc., Kansas City, MO; dated June 27, 1988.) MRID No. 407139-01.

APPROVED BY:

Robert J. Weir, Ph.D.
Program Manager
Dynamac Corporation

Signature: Robert J. Weir

Date: 4/21/89

1. CHEMICAL: Azinphos-methyl; O,O-dimethyl S-[(4-oxo-1,2,3-benzotriazin-3(4H)-yl)methyl]phosphorodithioate.

2. TEST MATERIAL: Azinphos-methyl (Guthion® Technical), batch No. 79-R-225-42/5FEB87, is a broad spectrum insecticide reported to be 87.7 percent pure.

3. STUDY/ACTION TYPE: Developmental toxicity study in rabbits.

4. STUDY IDENTIFICATION: Clemens, G. R., J. J. Bare, and R. E. Hartnagel. A teratology study in the rabbit with azinphos-methyl (Guthion® Technical). (Unpublished study No. MTD0070, conducted by Miles Inc., Elkhart, IN for Mobay Corporation, Inc., Kansas City, MO; dated June 27, 1988.) MRID No. 407139-01.

5. REVIEWED BY:

Patricia A. Turck, M.S.
Principal Reviewer
Dynamac Corporation

Signature: Patricia Turck
Date: April 24, 1989

James R. Plautz, M.S.
Independent Reviewer
Dynamac Corporation

Signature: Patricia Turck for James Plautz
Date: April 24, 1989

6. APPROVED BY:

Roman Pienta, Ph.D.
Department Manager
Dynamac Corporation

Signature: Roman J. Pienta
Date: april 24, '89

David Ritter
EPA Reviewer, Section I
Toxicology Branch II
(H7509C)

Signature: David Ritter
Date: 4-24-89

Mike Ioannou, Ph.D.
Acting EPA Section Head
Review Section I
Toxicology Branch II
(H7509C)

Signature: M. Ioannou
Date: 4-26-89

DATA EVALUATION REPORT

STUDY TYPE: Developmental Toxicity Guideline §83-3. TOX CHEM. NO.:

ACCESSION/MRID NUMBER: 407139-01.

TEST MATERIAL: Azinphos-methyl.

SYNONYMS: Guthion® Technical, 0,0-dimethyl S-[4-oxo-1,2,3-benzotriazin-3(4H)-yl)methyl]phosphorodithioate.

STUDY NUMBER: MTD0070.

SPONSOR: Mobay Corporation, Inc., Kansas City, MO.

TESTING FACILITY: Toxicology Department, Miles, Inc., Elkhart, IN.

TITLE OF REPORT: A Teratology Study in the Rabbit with Azinphos-methyl (Guthion® Technical).

AUTHOR(S): G. R. Clemens, J. J. Bare, and R. E. Hartnagel.

REPORT ISSUED: June 27, 1988.

CONCLUSIONS:

In a developmental toxicity study in which pregnant rabbits were administered oral doses of 0, 1.0, 2.5, or 6.0 mg/kg of azinphos-methyl on days 6 through 18 of gestation, inclusive, maternal toxicity as evidenced by cholinesterase inhibition and clinical signs was observed in animals given doses of 2.5 or 6.0 mg/kg/day. The maternal No-Observed-Effect Level (NOEL) was identified as 1.0 mg/kg/day, and the Lowest-Observed-Effect Level (LOEL) was 2.5 mg/kg/day.

A dose-related increase was observed in the incidence of fetuses and litters affected with lumbar and sacral vertebrae abnormalities (missing or extra arch; missing or extra centra) in the low- and mid-dose groups but not in the high-dose group. Additional historical control data are required before the developmental toxicity of azinphos-methyl can be assessed.

CLASSIFICATION: Core supplementary data.

A. MATERIALS

Test Compound: Purity: 87.7 percent
Description: Brown, waxy solid
Lot No.: 79-R-225-42/5FEB87
Contaminants: Not reported

Vehicle(s): 7 percent (v/v) aqueous EL-719P (Emulphor) obtained from GAF Corporation, New York, NY

Test Animals: Species: Rabbit
Strain: American Dutch
Source: Langshaw Farms, Augusta, MI
Age: males, 4 1/2 months; females, 6 1/2 months
Weight: males, 2.68 to 4.00 kg; females, 2.22 to 3.16 kg

B. STUDY DESIGN

This study was designed to assess the developmental toxicity potential of azinphos-methyl when administered orally by gavage from gestational days 6 through 18, inclusive.

Mating: Artificial insemination was employed over a 4-day period. Semen, collected from proven bucks and evaluated for motility and spermatozoa counts, was diluted in 0.9 percent sterile saline and administered intravaginally by pipette to randomly selected does. The does had been previously primed by intravenous (iv) human chorionic gonadotropin (HCG) injection (50 USP units) and received a second iv injection (100 USP units) concomitant with the pipetted semen. Day 0 of gestation was defined as the day on which insemination occurred.

Group Arrangement:

Test Group	Dose Level (mg/kg/day)[a]	Number Assigned
Control (aqueous Emulphor)	4 mL/kg	20
Low dose (LDT)	1.0	20
Mid dose (MDT)	2.5	20
High dose (HDT)	6.0	20

[a]Dosages are not corrected for the active ingredient.

Dosing: All doses were prepared daily during the dosing period and administered in a volume of 4 mL/kg of body weight. Doses were not adjusted for purity. Results of a range-finding study were provided to support a dose selection. Dosing volumes were administered based on body weight at day 6 of gestation.

Observations: The animals were checked for mortality or abnormal condition from days 0 through 28 of gestation. Maternal body weight was obtained on days 0, 6, 10, 14, 18, 21, and 28 of gestation. On day 19 of gestation, blood samples were collected to determine plasma and erythrocyte (RBC) cholinesterase (ChE) activities. Does were observed daily for overt changes in appearance and behavior and sacrificed on day 28 of gestation. Examinations at sacrifice consisted of:

- collection of blood samples for plasma and RBC ChE determinations;
- removal of the brain, which was divided into two sagittal sections, one-half of each section was immediately frozen on dry ice (for later enzyme analysis);
- brain, plasma, and RBC ChE activities were determined using a colorimetric method employing Ellmann's reagent, with acetylthiocholine as the substrate;
- number of corpora lutea was recorded;
- uteri and placentas were weighed, and number and position of resorptions and implantations were recorded;
- gross examination of doe's abdominal and thoracic viscera was performed, and any abnormalities were recorded; and
- total numbers of viable and nonviable fetuses were recorded.

The fetuses were examined in the following manner:

- complete external examination was performed;
- fetal weights were recorded;

- complete internal examination of viscera was conducted on all fetuses;
- sex was determined for all fetuses;
- cross-sectional cuts were made through the cerebral hemispheres to examine the brain; and
- skeletal development of all fetuses was studied using a modified Staples (KOH-Alizarin Red-S) method.

Statistical Analysis:

Dunnett's test - doe body weight, percent weight gain, actual (corrected) body weight and percent actual (corrected) weight gain, food consumption, and ChE activity.

Fisher's exact test, Kruskal-Wallis test - fertility index, gestation index, litter size, number of resorption sites, number and percent of viable fetuses, number and percent of nonviable fetuses, number of corpora lutea, percent male fetuses, mean fetal weight, number of implantations, preimplantation loss, postimplantation loss, mean placental weight.

Healy's test - mean fetal weight.

Chi-square test, Fisher's exact test, pairwise Fisher's exact test - all fetal skeletal structures with any changes were compared, as were fetal and litter incidence of malformations and select variations.

Compliance:

- A signed Statement of No Data Confidentiality Claim dated June 30, 1988 was provided.
- A signed Statement of Compliance with EPA GLP's dated June 24, 1988 was provided.
- A signed Quality Assurance Statement of Study Inspection dated June 23, 1988 was provided.

C. RESULTS

1. Maternal Toxicity

Mortality: One female from the mid-dose group and two females from the high-dose group were sacrificed on day 19 of gestation because of broken backs. All three were pregnant. No other deaths were noted.

Abortions: A total of one, zero, two, and zero females aborted in the control, low-dose, mid-dose, and high-dose groups, respectively. Prior to aborting on day 27 of gestation, the control doe (RS1594) was observed to have soft, little, or no stool on several occasions and a reddish-colored liquid discharge. In the mid-dose group, one female (RS1574) aborted on day 15, and the second (RS1584) aborted on day 27 of gestation. Neither doe from the mid-dose group exhibited any overt changes in appearance or behavior prior to aborting. These two abortions were probably not dose related since necropsy revealed pulmonary changes indicative of either dosing trauma and/or intercurrent respiratory infection.

Clinical Observations: Two to four animals from the high-dose group exhibited tremors and/or ataxia during the study. These clinical signs were not observed in any other test group or in controls, and were therefore considered to be compound related.

Body Weight: No compound-related adverse effect on body weight was observed during the study (Table 1). All values for the test groups compared favorably with the control group at every measurement interval throughout the study.

TABLE 1: Body Weight Gains and Corrected Body Weight Gains (kg ± S.D.)[a]

Dose Group (mg/kg/day)	Prior to Dosing Period (Day 0-5)	Dosing Period (Day 6-18)	Post-Dosing Period (Day 19-28)	Entire Gestation Period (Day 0-28)	Corrected[b] BW Gain Entire Gestation Period
0	0.07 ± 0.048	0.11 ± 0.095	0.04 ± 0.227	0.23 ± 0.254	0.15 ± 0.224
1.0	0 07 ± 0.390	0.14 ± 0.074	0.11 ± 0.102	0.31 ± 0.123	0.01 ± 0.125
2.5	0.06 ± 0.030	0.05 ± 0.136	0.05 ± 0.145	0.15 ± 0.134	0.20 ± 0.133
6.0	0.06 ± 0.055	0.12 ± 0.083	0.07 ± 0.181	0.25 ± 0.222	0.06 ± 0.232

[a]Data extracted from MTD0070, Appendices C and F. Only pregnant animals that survived to study termination are included.

[b]Corrected body weight gain for entire gestation period = body weight gain for entire gestation period minus gravid uterine weight.

Food Consumption: No compound-related adverse effects on food consumption were noted (Table 2). All groups compared favorably with the control group throughout the experiment.

TABLE 2. Summary of Food Consumption Data (g/animal/day)[a]

Dose Group (mg/kg/day)	Gestational day interval: 1 - 6	6 - 19	19 - 28
0	120 ± 12.1[b]	114 ± 19.2	83 ± 38.5
1.0	123 ± 9.7	113 ± 17.8	96 ± 25.5
2.5	125 ± 5.4	96 ± 30.4	70 ± 22.5
6.0	121 ± 11.6	116 ± 17.5	95 ± 36.7

[a]Data extracted from study No. MTD 0070, Table II, and Appendix C. Only pregnant animals that survived to study termination are included.

[b]Values are mean ± S.D.

Cholinesterase Determinations: Significant ($p \leq 0.05$) increases in the inhibition of both plasma and RBC ChE were observed at the mid- and high-dose levels on day 19 of gestation (Table 3). At day 28 of gestation, however, the only significant increase occurred in the high-dose group for brain ChE.

Gross Pathological Observations: No gross pathological changes were observed at necropsy that could be attributed to the administration of azinphos-methyl. A few does had gross pathologic changes which may have compromised reproductive status or fetal growth and development. One control female (RS1599) delivered seven viable fetuses that were below the average body weight for the rest of the group (25.4 g versus a group mean of 34.6 g). This doe had dilated, fluid-filled ventricles in the brain, a pale mottled liver, ulcers of the duodenum, and an empty gastrointestinal tract, as well as a decrease in body weight gain (-0.49 kg). Two females in the mid-dose group aborted during the study. Necropsy revealed that both of these animals had respiratory lesions; one female was apparently misdosed, and the other had pneumonia, adhesions to the pleural cavity and diaphragm, and serous fluid in the pleural cavity, in addition to a decrease in body weight gain prior to aborting.

TABLE 3. Summary of Percent Cholinesterase Inhibition in Rabbits Dosed with Azinphos-Methyl[a]

Dose Group (mg/kg/day)	Gestational day 19		Gestational day 28		
	Plasma	RBC	Plasma	RBC	Brain
0	0	0	0	0	0
1.0	0	13.8	0	0	4.3
2.5	13.0*	20.5	0	0	5.7
6.0	22.4*	50.1*	0	12.6	12.3*

[a]Data extracted from MTD0070, Table III and Appendix E.

*Significantly different from control at $p \leq 0.05$.

Cesarean Section Observations: A significant ($p \leq 0.01$) increase in preimplantation loss was noted in low- and high-dose does when compared to controls (Table 4). Although significantly higher than concurrent controls, the low dose was still within historical control range. In addition, the high preimplantation loss observed at the high dose was considered incidental by the authors because no evidence of this was found in two previous teratology studies using azinphos-methyl at similar or higher doses. Therefore, these findings were not considered to be compound related. The mean number of corpora lutea was greater and the mean number of implantations was less in the dosed groups than in controls. The changes, however, were not statistically significant.

Postimplantation loss was slightly higher (but not statistically significant) for dams given the high dose. A significant ($p \leq 0.05$) decrease in the number of pups/litter was observed at the high-dose level when compared to controls. In addition, a slight nonsignificant increase in the percentage of dead fetuses/dam was noted at the high dose level. Fetal weight and placental weight were not adversely affected by compound administration, but in the high-dose group, increases in fetal weight that were higher than expected in litters having fewer fetuses were noted. In fact, high-dose fetuses were approximately 15 percent heavier than controls. No other compound-related changes were observed.

2. Developmental Toxicity

External Examinations: No compound-related abnormalities were found upon external examination of fetuses. One control fetus had omphalocele, and one mid-dose fetus had microphthalmia (Table 5). No other external malformations or anomalies were observed.

Visceral Examinations: The only abnormality found upon examination of the viscera was dilation of cerebral ventricles in four control fetuses from one litter (Table 5). No abnormalities were reported in fetuses from dams administered azinphos-methyl.

Skeletal Examinations: Abnormal interparietals and supra-occipitals were found in five control fetuses from two litters (Table 6); these findings were not observed in

TABLE 4. Cesarean Section Observations[a]

Observation	Dose level (mg/kg/day) 0	1.0	2.5	6.0
No. animals assigned	20	20	20	20
No. animals mated/ inseminated	20	20	20	20
Pregnancy rate (%)	90	90	100	100
Maternal Wastage				
No. died[b]	0	0	1	2
No. died pregnant	0	0	1	2
No. nonpregnant	2	2	0	0
No. aborted	1	0	2	0
No. animals with live fetuses	17	18	17	18
Corpora lutea/dam	6.9	8.2	8.4	7.8
Implantations/dam	7.5	6.4	7.3	5.7
Preimplantation loss (%)[c]	1.5 ± 4.1[d]	23.0 ± 26.1**	14.8 ± 13.9	28.0 ± 22.6**
Postimplantation loss (%)[c]	2.4 ± 6.6	3.0 ± 7.3	4.3 ± 8.9	7.2 ± 12.9
Total No. live fetuses	124	112	118	97
No. live fetuses/dam	7.3 ± 1.4	6.2 ± 2.4	7.0 ± 1.7	5.5 ± 2.3*
Total No. resorptions	2	4	5	3
Resorptions/dam	0.12	0.22	0.29	0.17
Placental weight (g)*	5.2 ± 0.7	5.6 ± 0.8	5.2 ± 0.7	5.9 ± 0.7
Total No. dead fetuses	1	0	1	2
No. dead fetuses/dam	0.06	0	0.06	0.12
Mean fetal weight/ litter (g)*	34.6 ± 5.7	38.6 ± 5.3	35.1 ± 4.7	40.1 ± 5.6
Sex ratio (% male)*	51.6	53.6	45.8	56.7

[a]Data extracted from MTD0070, Tables IV and V and Appendix E.

[b]Animals sacrificed during the study because of broken backs.

[c]These values were recalculated by the reviewers and include data reported for pregnant animals that survived to terminal sacrifice only.

[d]Values are mean ± S.D.

*Values were calculated by the reviewers.

*Significantly different from control at $p \leq 0.05$.

**Significantly different from control at $p \leq 0.01$.

TABLE 5. External and Visceral Examinations[a]

Observation	Dose Level (mg/kg/day) 0	1.0	2.5	6.0
No. litters (fetuses) evaluated	17 (124)	18 (112)	17 (118)	18 (97)
External				
Omphalocele				
No. fetuses (%)	1 (0.81)	0	0	0
No. litters (%)	1 (5.88)	0	0	0
Microphthalmia				
No. fetuses (%)	0	0	1 (0.85)	0
No. litters (%)	0	0	1 (5.88)	0
Visceral				
Dilation of cerebral ventricles				
No. fetuses (%)	4 (3.23)	0	0	0
No. litters (%)	1 (5.88)	0	0	0

[a]Data extracted from MTD0070, Tables VI and IX.

TABLE 6. Summary of Skeletal Examinations[a]

Observation	Dose Level (mg/kg/day) 0	1.0	2.5	6.0
No. litters (fetuses) examined	17(124)	18(112)	17(118)	18(97)
Skull				
-Interparietal abnormal				
No. fetuses (%)	5(4.0)	0	0	0
No. litters (%)	2(11.8)	0	0	0
-Supraoccipital abnormal				
No. fetuses (%)	2(1.6)	0	0	0
No. litters (%)	1(5.9)	0	0	0
Vertebrae				
-Sacral arch missing				
No. fetuses (%)	2(1.6)	4(3.6)	7(5.9)	2(2.1)
No. litters (%)	2(11.8)	4(22.2)	7(41.1)	2(11.1)
-Sacral arch shift				
No. fetuses (%)	2(1.6)	3(2.7)	4(3.4)	1(1.0)
No. litters (%)	2(11.8)	3(16.7)	3(17.6)	1(5.5)
-Sacral centra missing				
No. fetuses (%)	2(1.6)	4(3.6)	7(5.9)	2(2.1)
No. litters (%)	2(11.8)	4(22.2)	7(41.1)	2(11.1)
-Lumbar arches extra				
No. fetuses (%)	2(1.6)	4(3.6)	7(5.9)	2(2.1)
No. litters (%)	2(11.8)	4(22.2)	7(41.1)	2(11.1)
-Lumbar centra extra				
No. fetuses (%)	2(1.6)	4(3.6)	7(5.9)	2(2.1)
No. litters (%)	2(11.8)	4(22.2)	7(41.1)	2(11.1)
Sternebrae				
-5th Bipartite				
No. fetuses (%)	0	6(5.4)*	0	0
No. litters (%)	0	6(33.3)	0	0
Metacarpals and phalanges				
-Right, missing				
No. (%) fetuses	0	1(0.89)	0	0
No. (%) litters	0	1(5.56)	0	0

[a]Data extracted from MTD0070, Tables VII and IX and Appendix G.
*Significantly different from controls at $p \leq 0.05$.

fetuses from dams receiving azinphos-methyl. Missing metacarpals and phalanges were found in one fetus from the low-dose group. Increased incidences (not statistically significant) in abnormalities of the spinal column were observed at the low- and mid-dose groups but not at the high-dose group when compared to controls. The litter incidences of missing sacral arch and centra were 11.8, 22.2, 41.1, and 11.1 percent for the control, low-, mid-, and high-dose groups, respectively. The observations of missing sacral arch and centra were associated with extra lumbar arch and centra in each case; each affected fetus had all four anomalies. Historical control data did not include information on these specific abnormalities. All other findings were distributed equally among control and test groups and were not considered to be compound related.

D. DISCUSSION/CONCLUSION:

a. Maternal Toxicity: Tremor and ataxia were observed in several does in the high-dose group. Statistically significant increases in the inhibition of plasma ChE at the mid-and high-dose level and RBC ChE at the high-dose level were noted on day 19 of gestation. In addition, a nonsignificant increase in the inhibition (20 percent) of RBC ChE activity was observed in animals in the mid-dose group on day 19 of gestation. On day 28 of gestation, brain ChE at the high-dose level was significantly increased. Based on the increased inhibition of plasma and RBC ChE at the mid- and high-dose levels on Day 19 of gestation, the maternal NOEL and LOEL were 1.0 mg/kg/day and 2.5 mg/kg/day, respectively.

b. Developmental Toxicity:

i. Death/Resorptions: An increase in preimplantation loss was observed in all dosed groups when compared to controls. However, only the high dose was outside the range of historical controls (28.0 percent and 5.0 to 16.2 percent for high-dose animals and historical controls, respectively). Since implantation generally occurs from days 6 through 9 of gestation, maternal toxicity associated with administration of the test material at 6.0 mg/kg/day may have caused a decrease in implantations. A significant decrease in the number of pups/litter was observed at the high dose. However, this was probably due to the significant increase in preimplantation loss and was not directly related

to test material administration.

ii. Altered Growth: Growth was not adversely affected by azinphos-methyl administration. Smaller litter sizes at the low- and high-dose levels resulted in higher mean fetal body weights (not statistically significant) at these doses.

iii. Developmental Anomalies: No compound-related effects were noted.

iv. Malformations: A nonsignificant increase in the incidences of fetuses and litters affected with spinal column abnormalities that included missing sacral arch and centra and extra lumbar arch and centra were observed in the low- and mid-dose groups but not in the high-dose group when compared to controls. Ignoring the high-dose group because of the observed maternal toxicity, a clear dose-related trend in the incidence of fetuses and litters affected with sacral and lumbar abnormalities was observed. The data suggest that the missing sacral structures were replaced with corresponding lumbar structures. However, since the investigators did not present historical control data on incidences of these specific abnormalities, a definitive assessment of these effects was not possible. Therefore, a NOEL and LOEL for the developmental toxicity was not established.

c. Study Deficiencies:

1) Individual data on fetal external and visceral findings were not presented. In addition, data on historical control incidences of missing sacral structures and extra lumbar structures was not presented.

2) Medians rather than means were reported for percent male fetuses, fetal body weight, and placental weight; median values may be a better representation of central tendency for a small data set because outliers have no effect on the value. However, for these data sets, the mean is a better indicator of central tendency.

3) The pregnancy status of does was apparently not confirmed using ammonium sulfide solution. Therefore, the reported pregnancy rates may be suspect.

E. CLASSIFICATION: Core Supplementary data.

Maternal NOEL = 1.0 mg/kg/day
Maternal LOEL = 2.5 mg/kg/day
Developmental Toxicity NOEL = not established
Developmental Toxicity LOEL = not established

The classification of this study can be upgraded upon submission of historical control data on spinal column abnormalities (missing sacral structures and extra lumbar structures).