FEB 6 2002

DATA EVALUATION RECORD

BAS 510 F/128008

STUDY TYPE: PRENATAL DEVELOPMENTAL TOXICITY STUDY - RABBIT [ORAL] [OPPTS 870.3700b (§83-3b); OECD 414

MRID 45404905

Prepared for

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

Prepared by

Toxicology and Hazard Assessment Group
Life Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37831
Task No. 02-06

Primary Reviewer:
Claudia M. Troxel, Ph.D.

Signature: Claudia M. Troxel
Date: FEB 0 6 2002

Secondary Reviewers:
Carol Forsyth, Ph.D., D.A.B.T.

Signature: Carol Forsyth
Date: FEB 0 6 2002

Robert H. Ross, M.S. Group Leader

Signature: Robert H. Ross
Date: FEB 0 6 2002

Quality Assurance:
Lee Ann Wilson, M.A.

Signature: L. A. Wilson
Date: FEB 0 6 2002

Disclaimer

This review may have been altered subsequent to the contractor's signatures above.

(1)

Oak Ridge National Laboratory is managed and operated by UT-Battelle, LLC., for the U.S. Department of Energy under Contract No. DE-AC05-00OR22725.

EPA Reviewer: Alan C. Levy, Ph.D.
Registration Action Branch 2, Health Effects Division (7509C)
EPA Work Assignment Manager: Ghazi Dannan, Ph.D.
Registration Action Branch 3, Health Effects Division (7509C)

Signature: Alan C. Levy
Date 7-23-2002
Signature: _____
Date _____

Template version 11/01

DATA EVALUATION RECORD
TXR#: 0050193

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

PC CODE: 128008

DP BARCODE: D278384
SUBMISSION NO.: S 604279

TEST MATERIAL (PURITY): BAS 510 F (94.4% a.i.)

SYNONYMS: none provided

CITATION: Schilling, K. and J. Hellwig (2000) BAS 510 F - Prenatal developmental toxicity study in Himalayan rabbits - oral administration (gavage). Experimental Toxicology and Ecology, BASF Aktiengesellschaft, 67056 Ludwigshafen/Rhein, FRG. Laboratory Project Identification: 40R0179/97127, July 26, 2000. MRID 45404905. Unpublished.

SPONSOR: BASF Corporation, Agricultural Products Division, RTP, NC 27709.

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 45404905), BAS 510 F (94.4% a.i., batch # N37) was administered to 25 Himalayan rabbits/dose by gavage at dose levels of 0, 100, 300, or 1000 mg/kg bw/day from gestation days (GDs) 7-28. On GD 29, does were sacrificed and subjected to gross necropsy. All fetuses were examined for external, visceral, and skeletal malformations/variations. The total numbers of fetuses examined (number of litters) was 135 (23), 183 (24), 145 (22), and 136 (21) for the 0, 100, 300, and 1000 mg/kg bw/day groups, respectively.

No clinical signs related to dose were observed. However, treatment-related maternal toxicity was observed in the high-dose group as evidenced by an increased number of abortions and early delivery and decreased food consumption. One high-dose doe delivered early, and 3 high-dose does aborted: two on GD 27 and one on GD 29. Statistically significant decreases ($p<0.05$; 0.01) were observed in mean absolute body weights on GD 28 and 29 (95% of controls); mean corrected terminal body weight (94% of controls); mean maternal body weight gains on GDs 7-9 (-22.9 g compared to -3.1 g) and GDs 21-23 (-10.3 g compared to 10.2 g); and mean corrected body weight change (-233.3 g vs. -125.3 g). High-dose animals also consumed less food than the controls starting with the commencement of treatment and continuing throughout the treatment period (52-90% of controls; generally statistically significant at $p<0.05$; 0.01).

2

Over the entire treatment interval of GD 7-28, the high-dose group consumed 26% less food than the controls ($p<0.05$; 0.01). Upon inspection of individual animal data, 4 does in particular were affected: the doe that delivered early, two of the does that aborted (on GD 27 or GD 29), and a fourth doe. These does started to exhibit drastic decreases in food consumption accompanied by decreases in body weight gain generally starting between GDs 14-16. The other doe that aborted on GD 27 did not exhibit consistent decrements in food consumption and body weight gain.

Other findings noted in the high-dose group and in the low- and mid-dose groups were not definitively related to treatment.

The maternal LOAEL is 1000 mg/kg bw/day based primarily on abortions or early delivery. The maternal NOAEL is 300 mg/kg bw/day.

Developmental toxicity was also evident in the high-dose group. As discussed, one high-dose doe delivered early, and 3 high-dose does aborted: two on GD 27 and one on GD 29. No treatment-related, statistically significant effects on pregnancy rates, number of corpora lutea, pre- or postimplantation losses, resorptions/dam, fetuses/litter, fetal body weights, or fetal sex ratios were observed in the treated groups as compared with the controls. One control and one mid-dose female had complete litter resorptions.

No treatment-related external, visceral, or skeletal malformations/variations were observed in any groups. Most treated and control litters contained fetuses with minor variations in skeletal ossification.

The developmental LOAEL is 1000 mg/kg bw/day based on increased number of abortions and early delivery. The developmental NOAEL is 300 mg/kg bw/day.

The developmental toxicity study in the rabbit is classified **Acceptable/Guideline** and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700; OECD 414) in the rabbit.

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

I. MATERIALS AND METHODS:

A. MATERIALS:

1. Test material: BAS 510 F

Description:	white powder
Lot/Batch #:	N 37
Purity:	94.4 % a.i.
Compound Stability:	four days in dosing solution
CAS # of TGAI:	188425-85-6
Structure:	

2. Vehicle and/or positive control: 0.5% Tylose (CB 30.000 in doubly distilled water) (Lot/Batch # and purity not provided)

3. Test animals:

Species:	Rabbit	
Strain:	Himalayan (CHbb:HM)	
Age/weight at study initiation:	34-36 Weeks old; 2200-3184 g; mean of ~ 2713 g	
Source:	Boehringer Ingelheim Pharma KG, Biberach an der Riss, Germany	
Housing:	singly in stainless steel wire mesh cages (floor area ~ 3000 cm)	
Diet:	Pelleted Kilba maintenance diet type 3418 for rabbits (Provimi Kliba Sa, CH-4303 Kaiseraugst, Switzerland) *ad libitum*	
Water:	Tap water *ad libitum* (water bottles)	
Environmental conditions:	**Temperature:**	20-24°C
	Humidity:	30-70%
	Air changes:	Information not provided
	Photoperiod:	12 Hrs dark/12 hrs light
Acclimation period:	At least 5 days	

B. PROCEDURES AND STUDY DESIGN

1. In life dates: Start: September 14, 1998; End: October 22, 1998

2. Mating: Female rabbits were injected intramuscularly with Receptal® about one hour before insemination. The rabbits were then inseminated with pooled ejaculate samples from male Himalayan rabbits of the same breed and housed under the same conditions as the females. The day of mating was designated as gestation day (GD) 0.

3. Animal Assignment: Animals were assigned randomly to dose groups as indicated in Table 1.

4

TABLE 1: Animal assignment

Dose (mg/kg bw/day)	0	100 (LDT)	300 (MDT)	1000 (HDT)
# Females	25	25	25	25

4. **Dose selection rationale:** No information was provided regarding the dose selection process. The authors stated that low-, middle-, and high-dose concentrations were expected to result in a no-observed-adverse-effect-level, an intermediate dose-level, and a level with some overt signs of maternal toxicity and possible developmental toxicity (and was the limit dose), respectively.

5. **Dosage preparation and analysis**: Test material-vehicle mixture was prepared at the beginning of the study, and thereafter at intervals of 1-3 days, by mixing appropriate amounts of test substance with 0.5% Tylose (CB 30.000 in doubly distilled water) using a high speed sonicator. The storage conditions of the test material-vehicle mixture were not described. Prior to the start of the study (approximately one year before), stability of the test substance in 0.5% Tylose CB 30.000 was evaluated for a period of 4 days at room temperature. Homogeneity (top, middle, and bottom) of the test mixture was evaluated before the beginning of the study (approximately one year before), and concentrations of the test mixture were evaluated before the beginning of the study (approximately one year before) and twice during the study period (beginning and near the end).

Results:

Homogeneity analysis: The mean concentrations of the samples taken from the top, middle, and bottom of the 6.0 and 10.0 g/100 mL test suspensions ranged from 90.0-93.3% of nominal and 95.0-99.0 % of nominal, respectively, indicating homogenous distribution of the test compound in the solutions.

Stability analysis: The mean concentrations of 50 mg/100 mL and 20 g/100 mL test suspensions at Day 4 as a percentage of nominal were 96.8% and 91%, respectively.

Concentration analysis: The mean concentrations of the 6.0, 8.0, and 10.0 g/100 mL test substance samples taken before study initiation ranged from 96.3 - 105.0% of nominal. The mean concentrations of the 1.0, 3.0, and 10.0 g/100 mL test substance samples taken near the beginning and end of the study ranged from 96.0 - 99.7% 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 28, in a volume of 10 mL/kg of body weight/day. Dosing was based on the last individual body weight.

C. OBSERVATIONS:

1. **Maternal observations and evaluations** - The animals were checked for mortality or clinical signs twice/day during the week and once/day on weekends and public holidays. Body weight data were recorded on gestation days 0, 2, 4, 9, 11, 14, 16, 19, 21, 23, 25, 28, and 29. Food consumption was determined daily. Dams were sacrificed on GD 29 and subjected to gross necropsy. The uterus and ovaries were removed, and the following data recorded: weight of the unopened uterus, number of corpora lutea and total implantations, and number and distribution of viable and nonviable fetuses and early and late resorptions. 5

2. **Fetal evaluations** - Each fetus was weighed and examined macroscopically for external findings, and placental weights were recorded. The abdomen and thorax of all fetuses were then opened, and the fetuses were sexed and examined internally for visceral abnormalities, with the heart and kidneys sectioned to assess internal structure. Next, the heads of approximately one-half of the fetuses/dam and of the fetuses with head malformations were severed, fixed in Bouin's, and processed and assessed according to Wilson's method. All fetuses were skinned and fixed in ethyl alcohol. The fetuses with heads were later removed from the fixative for a short period while cross sections of the heads were made to allow examination of the brain. After fixation in ethyl alcohol, all skeletons were stained according to a modified method of Dawson.

D. DATA ANALYSIS:

1. **Statistical analyses:** Simultaneous comparisons with the control group using Dunnett's test were used to evaluate food consumption; body weight, body weight change, corrected body weight gain, and carcass weights; weight of unopened uterus; number of corpora lutea, implantations, resorptions, and live fetuses; proportions of preimplantation loss, postimplantation loss, resorptions, and of live fetuses in each litter; litter mean fetal body weight; and litter mean placental weight. Female mortality, females pregnant at terminal sacrifice, and the number of litters with fetal findings were analyzed using a pairwise comparison of each dose group with the control using Fisher's Exact test (one-sided). Proportions of fetuses with malformations, variations, and/or unclassified observations in each litter were analyzed using pairwise comparison of each dose group with the control group using the Wilcoxon-test (one-sided).

   The statistical analyses employed by the study authors is not adequate. First, the homogeneity of variances needs to be evaluated to determine if parametric or nonparametric methods are appropriate. If testing indicates that the variances are homogeneous, an ANOVA analysis then needs to be run before proceeding with Dunnett's test to determine if there are any statistically significant differences between the means.

2. **Indices:** The following indices were calculated from cesarean section records of animals in the study:

   conception rate (%): $\frac{\text{number of pregnant animals}}{\text{number of fertilized animals}} \times 100$

   preimplantation loss (%): $\frac{\text{number of corpora lutea - number of implantations}}{\text{number of corpora lutea}} \times 100$

   postimplantation loss (%): $\frac{\text{number of implantations - number of live fetuses}}{\text{number of implantations}} \times 100$

3. **Historical control data:** Historical control data were provided to allow comparison with concurrent controls. Data were obtained from the control groups from 6 gavage studies and 2 intravenous studies in Himalayan rabbits conducted over a period of 3 years.

II. RESULTS:

A. MATERNAL TOXICITY:

1. **Mortality and clinical observations:** One control and one mid-dose doe were found dead on GD 22 and 19, respectively. The deaths were the result of gavage error. One mid-dose female and 3 high-dose females were killed after aborting, and another high-dose female was killed after early delivery (day 29). A few days prior to aborting on GD 27, one high-dose female exhibited discolored feces and reduced defecation, while the mid-dose female showed reduced defecation. The remaining females that aborted or delivered early did not show any clinical signs. No substance-related clinical signs were observed in other females.

2. **Body weight** - Body weight data are summarized in Table 2. The high-dose group had statistically significant decreases ($p<0.05$) in mean absolute body weights on GD 28 and 29 (95% of controls) and mean corrected terminal body weight (94% of controls). The high-dose group also had statistically significant decreases ($p<0.05$; 0.01) in mean body weight gain on GDs 7-9 (-22.9 g compared to -3.1 g), GDs 21-23 (-10.3 g compared to 10.2 g), and over the entire treatment period of GDs 7-28 (19% of controls), and in the mean corrected body weight gain (corrected terminal body weight - GD 7 body weight; -233.3 g compared to -125.3 g). The low-dose group also exhibited a significant decrease in mean corrected body weight gain (-220.6 g compared to -125.3 g). Other statistically significant body weight changes in other groups occurred before initiation of dosing. Individual rabbit body weight gain was over a relatively large range as evidenced by the size of the standard deviations.

   Upon inspection of individual animal data, the mid-dose doe that aborted exhibited decreases in absolute body weight and body weight gain as compared to the group mean. In the high-dose group, 4 does in particular were affected: the doe that delivered early, two of the does that aborted (on GD 27 or GD 29), and a fourth doe (doe # 80). The decreases in body weight gain in all four of these animals generally became severe starting at GD 14-16. The other high-dose doe that aborted on GD 27 did not exhibit consistent decrements in body weight gain.

TABLE 2. Mean (±SD) maternal body weight gain (g) [a]

Interval	Dose in mg/kg bw/day			
	0	100	300	1000
Pretreatment: GD 0 - 7	11.0 ± 60.2	53.9* ± 58.9	31.6 ± 57.7	41.5 ± 49.4
Treatment: GD 7-28	146.8 ± 120.9	125.5 ± 96.3 (85)[b]	115.0 ± 114.7 (78)	27.8** ± 182.3 (19)[c]
Corrected BW Gain: GD 7-28	-125.3 ± 91.6	-220.6** ± 88.9	-190.3 ± 100.9	-233.3** ± 141.9

[a] Data obtained from Tables Ia, pages 63-64; MRID 45404905.
[b] Percentage of controls; calculated by reviewer
c Two animals lost 387 and 523 g; all others were in the range of -54 to +254 g; excluding the 387 and 523 values, the group mean was 76.8 g.
* Statistically different ($p<0.05$) from the control.
** Statistically different ($p<0.01$) from the control.

3. **Food consumption**: Food consumption data are summarized in Table 3. High-dose animals consumed less food than the controls starting with the commencement of treatment and continuing throughout the treatment period (52-90% of controls). Generally, these differences attained statistical significance ($p<0.05; 0.01$). Over the entire treatment interval of GD 7-28, high-dose animals consumed 26% less food than controls ($p<0.05$ as calculated by reviewer using ANOVA followed by Dunnett's test). The low- and mid-dose groups each had one time period when food consumption was statistically decreased compared to controls.

   When inspecting individual food consumption data, the mid-dose doe that aborted had reduced food consumption starting with GD 0-1 and continuing throughout the study. Starting at GD12-13 and continuing at daily intervals, food consumption ranged from 0.0-2.7 g/animal/day. Although other individual animals from the mid-dose group exhibited occasional drastic decreases in food consumption, these decreases were sporadic. In the high-dose group, 4 does in particular were affected: the doe that delivered early, two of the does that aborted (on GD 27 or GD 29), and a fourth doe (doe # 80). These does generally had food consumption values comparable to the group mean until GD14-15 or 15-16, after which food consumption was generally less than 5.0 g/day. The food consumption of the other doe that aborted on GD 27 was decreased compared to the group mean starting on GD 22-23, but these decreases where well within the standard deviations of the group mean.

TABLE 3. Selected Mean (±SD) Maternal Food Consumption (g/animal/day) [a]

Interval	Dose in mg/kg bw/day			
	0	100	300	1000
Pretreatment: GD 0 - 7	95.0 ± 5.2	98.7 ± 6.4	93.2 ± 5.2	92.3 ± 4.2
GD 7-8	85.1 ± 19.4	89.5 ± 24.2	76.1 ± 25.6 (89)[b]	50.6** ± 20.7 (59)
GD 17-18	78.6 ± 16.9	61.0 ± 29.1	59.1* ± 31.6 (75)	50.5** ± 32.0 (64)
GD 27-28	75.5 ± 21.0	72.3 ± 16.8	77.2 ± 19.5	59.9* ± 25.2 (79)
Treatment: GD 7-28	76.1 ± 7.3	69.0 ± 13.4 (91)	68.3 ± 10.4 (90)	56.2+ ± 11.1 (74)

[a] Data obtained from Tables IA, pages 55-58; MRID 45404905.
[b] Percentage of controls; calculated by reviewer
* Statistically different ($p<0.05$) from the control.
** Statistically different ($p<0.01$) from the control.
+ Statistically different ($p<0.05$) from the control (calculated by reviewer using ANOVA followed by Dunnett's test).

4. **Gross pathology:** The one control and one mid-dose doe that were found dead on GD 22 and 19, respectively, had serous or bloody fluid in the thoracic cavity, a finding consistent with gavage error. These does also had pulmonary congestion, with the mid-dose doe additionally exhibiting pulmonary edema. Of the does that aborted or delivered early, the mid-dose doe showed lung congestion, two of the high-dose does exhibited no abnormalities, one high-dose doe exhibited lung congestion and a light brown-gray liver, and one high-dose doe had consolidated lungs, light brown-gray liver, fatty degeneration of the kidney, and hydronephrosis. Other gross necropsy findings were equally distributed amongst the groups. Of particular note, however, was that lung congestion was observed in 2, 6, 6, and 4 does

from the 0, 100, 300, and 1000 mg/kg bw/day groups, respectively (these values include all does).

5. **Cesarean section data** - Data are summarized in Table 4. One mid-dose doe aborted on GD 26, three high-dose does aborted (two on GD 27 and one on GD 29), and one high-dose doe delivered early (day 29). No abortions or early deliveries were observed in the control or low-dose group. No other parameters appeared to have been adversely effected by BAS 510 F.

TABLE 4. Cesarean section observations [a]

Observation	Dose (mg/kg bw/day)			
	0	100	300	1000
# Animals Assigned (Mated)	25	25	25	25
# Animals Pregnant	25	24	25	25
Pregnancy Rate (%)	100	96	100	100
# Nonpregnant	0	1	0	0
Maternal Wastage				
# Died	1	0	1	0
# Died Pregnant	1	0	1	0
# Died Nonpregnant	0	0	0	0
# Aborted	0	0	1	3
# Premature Delivery	0	0	0	1
Total # Corpora Lutea	209	220	197	192
Corpora Lutea/Dam	8.7 ± 1.7	9.2 ± 1.6	8.6 ± 2.0	9.1 ± 1.5
Total # Implantations	164	199	177	153
(Implantations/Dam)	6.8 ± 2.3	8.3* ± 1.7	7.7 ± 2.2	7.3 ± 2.1
Total # Litters	23	24	22	21
Total # Live Fetuses	135	183	145	136
(Live Fetuses/Dam)	5.9 ± 2.3	7.6* ± 1.6	6.6 ± 2.1	6.5 ± 2.5
Total # Dead Fetuses	0	0	0	0
(Dead Fetuses/Dam)	0	0	0	0
Total # Resorptions	29	16	32	17
Early	22	14	25	11
Late	7	2	7	6
Resorptions/Dam	1.2 ± 1.4	0.7 ± 1.1	1.4 ± 2.5	0.8 ± 0.8
Early	0.9 ± 1.1	0.6 ± 1.1	1.1 ± 2.3	0.5 ± 0.8
Late	0.3 ± 0.9	0.1 ± 0.3	0.3 ± 0.6	0.3 ± 0.5
Litters with Total Resorptions	1	0	1	0
Mean Fetal Weight (g)	36.5 ± 3.7	34.9 ± 4.0	37.3 ± 3.6	34.9 ± 6.3
Males	36.2 ± 3.9	34.8 ± 3.7	37.2 ± 3.9	34.9 ± 6.5
Females	36.4 ± 3.9	35.0 ± 4.7	36.6 ± 4.0	34.4 ± 6.2
Sex Ratio (% Male)	46.7	52.5	45.5	43.4
Preimplantation Loss (%)	22.5 ± 19.6	9.5* ± 9.8	9.9* ± 15.0	20.2 ± 19.0
Postimplantation Loss (%)	19.9 ± 26.2	7.7 ± 12.4	16.8 ± 27.9	14.2 ± 16.6
Mean Gravid Uterine Weight (g)	288.1 ± 117.9	359.7* ± 63.9	320.5 ± 110.2	298.4 ± 87.9
Mean Placental Weight (g)	4.2 ± 0.9	4.1 ± 0.5	4.3 ± 0.7	4.0 ± 1.0

[a] Data obtained from Table 1A and 1B, pages 64, 67- 71; MRID 45404905.
* Statistically different ($p < 0.05$) from the control.

B. DEVELOPMENTAL TOXICITY:

1. **External examination**: Findings from external examination are presented in Table 5a. No treatment-related malformations/variations were noted during external examination of fetuses.

2. **Visceral examination**: Selected findings from visceral examination are presented in Table 5b. No effects appeared to be related to test article administration.

3. **Skeletal examination**: Selected findings noted during skeletal examination are presented in Table 5c. Skeletal malformations occurred in low incidence and in a non-dose related manner. The high-dose group had a statistically increased litter incidence of incomplete ossification of the thoracic centrum.

TABLE 5a. External examinations [a]

Observations [b]	Dose (mg/kg bw/day)			
	0	100	300	1000
#Fetuses(litters) examined	135 (23)	183 (24)	145 (22)	136 (21)
#Fetuses(litters) affected with malformations	0 (0)	1 (1)	2 (2)	0 (0)
Meningoencephalocele and Microcephaly	0 (0) [c]	0 (0)	1 (1)	0 (0)
Spina bifida	0 (0)	1 (1)	0 (0)	0 (0)
Thread-like tail	0 (0)	0 (0)	1 (1)	0 (0)
#Fetuses(litters) affected with variations	5 (4)	4 (3)	4 (4)	2 (2)
Paw hyperflexion	5 (4)	4 (3)	4 (4)	2 (2)

[a] Data obtained from Table IB, pages 72-76; MRID 45404905.
[b] Some observations may be grouped together.
[c] Fetal (litter) incidence

TABLE 5b. Visceral examinations [a]

Observations [b]	Dose (mg/kg bw/day)			
	0	100	300	1000
#Fetuses(litters) examined	135 (23)	183 (24)	145 (22)	136 (21)
#Fetuses(litters) affected with malformations	5 (4)	5 (5)	3 (2)	0 (0)
Muscular ventricular septum defect	4 (3) [c]	3 (3)	1 (1)	0 (0)
#Fetuses(litters) affected with variations	7 (6)	15 (9)	9 (4)	12 (9)
Malpositioned carotid branch	7 (6)	15 (9)	9 (4)	12 (9)

[a] Data obtained from Table IB, pages 77-84; MRID 45404905.
[b] Some observations may be grouped together.
[c] Fetal (litter) incidence

TABLE 5c. Skeletal examinations [a]				
Observations [b]	Dose (mg/kg bw/day)			
	0	100	300	1000
#Fetuses(litters) examined	135 (23)	183 (24)	145 (22)	136 (21)
#Fetuses(litters) affected with malformations	2 (2)	5 (3)	5 (4)	2 (2)
Absent lumbar vertebra	0 (0) [c]	2 (2)	0 (0)	1 (1)
Misshapen scapula	0 (0)	1 (1)	1 (1)	1 (1)
Bony plate (sternebrae severely fused)	1 (1)	0 (0)	2 (2)	0 (0)
#Fetuses(litters) affected with variations	82 (21)	127 (24)	86 (21)	84 (19)
Incomplete ossification of thoracic centrum	1 (1)	4 (4)	6 (3)	16 (7)*

[a] Data obtained from Table IB, pages 85-99; MRID 45404905.
[b] Some observations may be grouped together.
[c] Fetal (litter) incidence
* Statistically different ($p < 0.05$) from the control.

III. DISCUSSION AND CONCLUSIONS:

A. **INVESTIGATORS' CONCLUSIONS:** The investigators concluded that maternal toxicity was evident in the mid- and high-dose group. In the mid-dose group, maternal toxicity was indicated by one doe aborting following a few days of reduced defecation. In the high-dose group, maternal toxicity was evidenced by 3 does aborting and one doe delivering early, discolored feces and reduced defecation in one of these does a few days prior to aborting, and statistically decreased food consumption, body weight and body weight gain, corrected body weight gain, and corrected terminal body weight. No dose-related effects on fetal development were observed. Therefore, the NOAEL for maternal toxicity is 100 mg/kg bw/day, while it is 1000 mg/kg bw/day for developmental toxicity.

B. **REVIEWER COMMENTS:**

1. **Maternal toxicity:** The deaths occurring in the one control and one mid-dose doe were attributed to gavage error. It appears from the slightly elevated incidence of lung congestion seen in all groups (2, 6, 6, and 4 does, respectively) that there may have been some laboratory error in gavage administration, but it was not enough of a technique error to result in compromised study results.

   The mid-dose doe (number 63) that aborted on GD 26 appeared to be in compromised health from the beginning of the study. This doe had decreased food consumption from GD 1, before the test substance was administered. These decrements in food consumption became more severe as the study progressed, and were accompanied by decreases in absolute body weight and body weight gain. Therefore, the effects noted in this doe are not considered to have been attributable to treatment with BAS 510 F.

   Maternal toxicity was present in the high-dose group. One doe delivered early (day 28), and 3 does aborted. It was noted that one of the does that aborted exhibited discolored feces and reduced defecation a few days prior to aborting. The relevance of these signs in relation to substance administration is not known. No other clinical signs related to dose were observed. The high-dose group had statistically significant decreases in mean maternal body weight gain and mean food consumption for the treatment interval of GD 7-28. Upon inspection of

individual animal data, 4 does in particular were affected: the doe that delivered early, two of the does that aborted (on GD 27 or GD 29), and a fourth doe. These does started to exhibit dramatic decreases in food consumption accompanied by significant decreases in body weight gain generally starting between GDs 14-16. The other doe that aborted on GD 27 did not exhibit consistent decrements in food consumption and body weight gain. Because of the relatively wide range of body weight gains (large standard deviations), it is not considered that any of the doses of BAS 510 F resulted in a toxicologically significant effect on body weights or gains.

Therefore, the maternal toxicity LOAEL is 1000 mg/kg bw/day based primarily upon abortions or early delivery. The maternal NOAEL is 300 mg/kg bw/day.

2. **Developmental toxicity:**

   a. **Deaths/resorptions:** One abortion was observed in the mid-dose group, and 3 abortions and an early delivery were noted in the high-dose group. The single abortion observed in the mid-dose group is not attributed to treatment because the health of the animal appeared to have been compromised even before the initiation of treatment. Two of the abortions and the early delivery occurring in the high-dose group are likely the result of maternal toxicity as evidenced by significant decrements in food consumption and body weight gain. No abortions or early deliveries were observed in the control or low-dose group.

   b. **Altered growth:** Although the high-dose group had a statistically increased litter incidence of incomplete ossification of thoracic centrum, no other evidence of delayed fetal growth (such as decreased fetal weights or other significant effects on ossification) were observed. Therefore, this fetal variation is not considered to have been attributable to treatment. It was concluded that treatment did not result in any alterations of fetal growth.

   c. **Developmental variations:** No adverse, treatment-related increases in developmental variations were observed.

   d. **Malformations:** Maternal treatment with BAS 510 F did not result in any substance-related major fetal malformations.

Therefore, the developmental toxicity LOAEL is 1000 mg/kg bw/day based upon increased number of abortions and early delivery, and the developmental NOAEL is 300 mg/kg bw/day.

C. **STUDY DEFICIENCIES:** Minor deficiencies include that the dose selection rationale was not provided and no information about the storage of the test substance was given. These deficiencies do not compromise the study because having the missing information and data available would not have changed any of the conclusions of the study. A more significant deficiency is that the statistical method was not adequate (i.e., no test for homogeneity of variance or ANVOA). Despite the inadequacy of the analyses, however, the differences

noted in the study were biologically significant. Therefore, the conclusions of the study would not be altered by a statistical reanalysis of the data.

DATA FOR ENTRY INTO ISIS

Developmental Study - rabbits (870.3700b)

PC code	MRID	Study	Species	Duration	Route	Admin	Dose range mg/kg/day	Doses mg/kg/day	NOAEL mg/kg/day	LOAEL mg/kg/day	Target organ	Comments
128008	45404905	developmental	rabbits	GD 7-28	oral	gavage	100-1000	0, 100, 300, 1000	300	1000	body weight and food consumption decreasc	Maternal
128008	45404905	developmental	rabbits	GD 7-28	oral	gavage	100-1000	0, 100, 300, 1000	300	1000	abortions/early delivery	Developmental